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Lifestyle Factors and Risk of Heart Failure: A Prospective Cohort Study

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LIFESTYLE FACTORS AND RISK OF HEART FAILURE: A PROSPECTIVE COHORT STUDY

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To my parents, my husband and my baby

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ABSTRACT

Heart failure (HF) has become a major health problem with its high prevalence, poor clinical outcomes, and large health-care costs. Compared with medical intervention, the prevention of HF through lifestyle approaches is free of side effect. Therefore, the prevention of HF through lifestyle approaches is of special interest. In this project, we aim to investigate 1) the association of different levels of occupational, commuting and leisure-time physical activity with HF risk; 2) the association of coffee consumption with HF risk; 3) the role of lifestyle factors in explaining the risk of HF; and 4) the association between antihypertensive drug treatment and HF risk with the association between engaging in a healthy lifestyle and HF risk.

We conducted prospective studies among Finnish men and women who were 25 to 74 years of age and free of HF at baseline. Cox proportional hazards regression models were used to estimate the associations of interest. Partial population attributable risk was calculated to estimate the proportion of new HF cases occurring in this population that hypothetically could have been prevented if all subjects had certain health lifestyle factors.

Our study results showed that 1) moderate and high levels of occupational or leisure-time physical activity are associated with a reduced risk of HF in both sexes; A simultaneous engagement in two or three types of physical activity showed a slightly stronger protective effect than participation in only one type of physical activity; 2) coffee consumption does not increase the risk of HF in Finnish men and women; In women, we observed an inverse association between low-to-moderate coffee consumption and the risk of HF; 3) maintaining a body mass index $\leq$25, consuming vegetable $\geq$3 times a week,

abstaining from smoking and engaging in moderate or high level of physical activity were individually and jointly associated with a decreased risk of HF among both men and women; The relationship between the number of healthy lifestyle factors one engaged in and HF risk was dose-response; and 4) HF risk was lower in hypertensive patients who engaged in a healthy lifestyle but higher in hypertensive people using antihypertensive drug treatment.

CHAPTER 1. OVERVIEW

1.1 Introduction

Heart Failure (HF) has emerged as a major and growing health problem both in the developed and developing regions of the world.(Schocken et al., 2008a) Although use of medication has reduced re-hospitalization rates and mortality from HF,(Lee et al., 2004) it remains the leading cause of hospitalization for older people in the United States.(Kozak et al., 2006) Mortality among HF patients remains substantial. About one quarter of patients died within one year of diagnosis and half died within five years of diagnosis.(Levy et al., 2002; Roger et al., 2004) Therefore, the prevention of HF through lifestyle approaches is of special interest. The association of lifestyle factors with HF risk will be evaluated in the studies described in this application using the FINRISK Study, conducted in Finland.

The FINRISK Study is one of the largest prospective epidemiological studies of chronic disease risk factors in the world. The total sample consists of 62,013 randomly selected individuals (30,031 men and 31,982 women) aged 25-74 years. Baseline data collections include medical history, socio-economic factors, lifestyle factors, and the direct measurements of height, weight, blood pressure, and serum total cholesterol. The follow-up is virtually complete through the nationwide register linkage. During a mean follow-up of 18.4 years, 1992 men and 1771 women developed incident HF. Thus, this is one of the largest prospective studies of HF in the world. The existing data and data which will be generated during further follow-up of this cohort provide a unique opportunity to identify potential preventive strategies for HF.

Specifically, we provide detailed evaluations of the following research questions in this dissertation:

Research Questions

1. Does physical activity during occupation, commuting, and/or leisure time decrease HF risk?
2. Does coffee consumption influence the risk of HF?
3. What are the joint effects of lifestyle factors (physical activity, alcohol consumption, coffee consumption, smoking, and obesity) on the risk of HF?
4. Whether there are differences in HF risk among hypertensive men and women using antihypertensive drug treatment at baseline versus those engaging in a healthy lifestyle at baseline?

Hypotheses

1. Physical activity during occupation, commuting, and/or leisure time decrease HF risk.
2. Coffee consumption influences HF risk.
3. Lifestyle factors (physical activity, alcohol consumption, coffee consumption, smoking, and obesity) influences HF risk.
4. Differences exist in HF risk among hypertensive men and women using antihypertensive drug treatment at baseline versus those engaging in a healthy lifestyle at baseline

Justification

According to the World Health Organization (WHO), the knowledge about the epidemiology, risk factors, prognosis, treatment, and prevention of coronary heart disease (CHD) and stroke has been investigated more systematically than that of HF because only a few population-based epidemiologic studies are available for HF.(World Health Organization) Data from a few population-based epidemiologic studies in the US and Europe have provided evidence that lifestyle factors play an important role in the etiology of HF.(He et al., 2001; Kannel et al., 1999; Schocken et al., 2008a) Thus, the prevention of HF through lifestyle approaches is possible. In order to determine interventions that would prevent or delay the onset of HF, identification of modifiable risk factors for HF is indispensable because these risk factors could then be used as targets for intervention. Therefore, independent confirmation and further exploration of lifestyle factors with the risk of HF in well-designed large prospective studies will provide crucial information for us to gain a better understanding of the complex lifestyle-HF relationships.

The present study, which is part of the FINRISK study, utilized a prospective cohort design. The subjects involved in this study were general population of Finland. The study sample was nationally representative. The present study would provide important information for understanding the causes and prevention strategies of HF.

Limitations

1. Study cohorts represented random samples of Finnish men and women. However, results of the present study may not be able to generalize to other populations.

2. Even though we gathered data on several potential confounders such as age, education, blood pressure, total cholesterol etc., residual confounding due to measurement error in the assessment of confounding factors, or some unmeasured dietary factors were not determined thus, cannot be excluded.
3. All exposure and covariate information was measured at baseline surveys prior to HF diagnoses. We have no data on possible changes in these factors during the follow-up. The misclassification of the levels of these factors during the follow-up is most probably not systematically related to the outcome, but may weaken the observed association.

1.2 Review of literature

Epidemiology of HF

HF has emerged as a worldwide epidemic and is one of the leading causes of morbidity and mortality for old people in the US and other Western countries.(He et al., 2001; Nieminen and Harjola, 2005) According to the estimation of American Heart Association (AHA), 550,000 new cases occur each year, and more than 5 million Americans have HF.(Schocken et al., 2008a) According to the estimation of the European Society of Cardiology (ESC), 10 million people have HF in the Europe, and HF patients accounts for 0.4% to 2% of the general European population.(Nieminen and Harjola, 2005) In addition, HF has put a heavy economic burden on the society. An estimated of > $33 billion was spent on HF in 2007 according to AHA.(Schocken et al., 2008a)

Overweight/obesity, physical activity and HF[1]

The epidemic of unhealthy lifestyle habits including, overweight/obesity and sedentary lifestyle has serious public health and economic consequences. Obesity, which may be caused by unhealthy diet and/or physical inactivity, has long been regarded as a major public health problem in the US(Allison et al., 1999). The data from a community-based study conducted among subjects aged 65 years and over living in New Haven has shown that obesity, as assessed by body mass index (BMI: calculated as weight [kilogram] divided by height squared [square meter]) ≥28, is a predictor for HF risk.(Chen et al., 1999) This finding has been confirmed by many other studies.(Bahrami et al., 2008; He et al., 2001; Hu et al.; Ingelsson et al., 2005b; Ingelsson et al., 2005c; Kenchaiah et al., 2002; Kenchaiah et al., 2009; Levitan et al., 2009a; Loehr et al., 2009; Nicklas et al., 2006) It was not until recent years that scientists began to include the indexes of abdominal obesity: waist circumference (WC), waist-to-hip ratio (WHR: WC [centimeter] divided by hip circumference [centimeter]), waist-height ratio (WHtR: WC [centimeter] divided by height [centimeter]) and waist-to-thigh ratio (WTR: WC [centimeter] divided by thigh circumference [centimeter]) into their studies.(Bahrami et al., 2008; Hu et al., 2010b; Ingelsson et al., 2005c; Levitan et al., 2009a; Loehr et al., 2009; Nicklas et al., 2006) These studies reveal that these indexes are also predictors of HF risk. Prospective epidemiological studies that investigated the association between obesity and HF were summarized in table 1. The results from these prospective studies consistently indicate that both general obesity and abdominal obesity increase the risk of HF.

The increase in computerization and mechanization during the last decades has resulted in

[1] This section originally appeared as Yujie Wang and Gang Hu. The individual and joint associations of obesity and physical activity on the risk of heart failure. Congestive Heart Failure, 16(6), 292-299, 2010. Reprinted by permission of John Wiley and Sons. http://onlinelibrary.wiley.com/doi/10.1111/j.1751-7133.2010.00189.x/abstract

ever-increasing numbers of people being sedentary for most of their time. In the US, more than one half of the adults do not engage in physical activity at the level currently recommended for health promotion.(Pate et al., 1995; Thompson et al., 2003) In response to this severe situation, three studies have looked into the association between regular physical activity and HF risk.(He et al., 2001; Hu et al., 2010b; Kenchaiah et al., 2009) Prospective epidemiological studies that investigated the association between physical activity and HF were summarized in table 2. The results from these prospective studies consistently indicate that regular physical activity reduces the risk of HF. However, most previous studies focused on leisure time physical activity alone and the evidence on other types of physical activity, such as occupational or commuting physical activity, is sparse. It is unclear whether different forms of physical activity are independently related to a reduced risk of incident HF, and the joint effects of different types of physical activity would reduce the risk of HF further.

Coffee consumption and HF

Coffee is one of the most widely consumed beverages in the world.(Popkin et al., 2006) It has been suggested that coffee consumption may be associated with the risk of coronary heart disease (CHD),(Wu et al., 2009) hypertension,(Corti et al., 2002; Jee et al., 1999; Lovallo et al., 2004; Noordzij et al., 2005; Winkelmayer et al., 2005) and lower risk of type 2 diabetes,(Tuomilehto et al., 2004; van Dam and Hu, 2005)all of which are known risk factors of HF.(Ho et al., 1993; Kannel et al., 1974; Levy et al., 1996) Two prospective studies have previously investigated the association between coffee consumption and HF risk among Swedish men.(Ahmed et al., 2009; Wilhelmsen et al., 2001) The first prospective study on the relation between coffee consumption and the risk of HF was conducted among

Table 1. Selected findings on the association between obesity and the risk of heart failure

Author, year	No. of heart failure cases /No. of participants*	Age range (years)	Follow-up	Major findings, BMI (kg/m2) Hazard ratios (95% CI)	Adjustment factors
General obesity					
Chen et al, 1999(Chen et al., 1999)	173 (85M/88F) /1749 (718M/1031F)	≥65	10-year	BMI <24, HR 1.00 (reference) BMI 24-27.9, HR 1.1 (0.7-1.7) BMI ≥28, HR 1.8 (1.1-2.7)	Sex, age, DM, pulse pressure, MI during follow-up, and type of housing
He et al，2001(He et al., 2001)	1382 (741M/641F） /13643(5545M/8098F)	25-74	19-year	Male BMI <27.8, HR 1.00 (reference) BMI ≥27.8, HR 1.23 (1.00-1.52) Female BMI <27.3, HR 1.00 (reference) BMI ≥27.3, HR 1.34 (1.10-1.64)	Age, race, education level, smoking, regular alcohol consumption, SBP, low physical activity, hypertension, history of DM, history of valvular heart disease, and history of CHD
Kenchaiah et al, 2002(Kenchaiah et al., 2002)	496 (238M/258F) /5881(2704M/3177F)	55 (mean)	14-year	each 1-unit increase in BMI Male, HR 1.05 (1.02-1.09) Female, HR 1.07 (1.04-1.10)	Alcohol consumption, serum total cholesterol, presence or absence of current smoking, valve disease, hypertension, DM, ECG-LVH, and MI

Table 1 continued

Ingelsson et al, 2005(Ingelsson et al., 2005c)	104M/1187M	≥70	8.9-year (median)	each 1-SD increase in BMI HR 1.35 (1.11-1.65)	DM, prior MI, hypertension, ECG-LVH, smoking, and serum cholesterol
Ingelsson et al, 2005(Ingelsson et al., 2005b)	259M/2321M	≥50	28.8-year (median)	each 1-SD increase in BMI HR 1.47 (1.31-1.65)	Prior acute MI, hypertension, DM, ECG-LVH, smoking, and serum cholesterol
Nicklas et al, 2006(Nicklas et al., 2006)	166 (73M/93F)/ 2435 (1081M/1354F)		6.1-year (median)	each 1-SD increase in BMI HR 1.25 (1.02-1.53)	Age, sex, race, site, education, smoking, chronic obstructive pulmonary disease, inflammation, incident MI, homeostasis model assessment of insulin sensitivity index, DM, and hypertension
Bahrami et al, 2008(Bahrami et al., 2008)	79/6814 (3204M/3610F)	45-84	4-year (median)	BMI <30, HR 1.00 (reference) BMI ≥30, HR 1.83 (1.14-2.92)	Age, gender, hypertension, DM, LVH, Serum total cholesterol, and current smoking,
Loehr et al, 2009(Loehr et al., 2009)	1528(825M/703F) /14641(6632M/8009F)	45-65	16-year (median)	each 1-SD increase in BMI Male, HR 1.47 (1.39-1.57) Female, HR 1.49 (1.39-1.59)	Age, alcohol use, educational level, smoking status, and center

Table 1 continued

Kenchaiah et al, 2009(Kenchaiah et al., 2009)	1109M/21094M	40-84	20.5-year	BMI <25, HR 1.00 (reference) BMI 25-29.9, HR 1.49 (1.32-1.69) BMI ≥30, HR 2.80 (2.24-3.50)	Age, smoking, alcohol consumption, parental history of MI, random assignment to aspirin or β-carotene, vigorous physical activity, history of hypertension, DM, and hypercholesterolemia
Levitan et al, 2009(Levitan et al., 2009a)	1100 (718M/382F) /80360(43487M /36873F)	45-79M /48-83F	7-year (median)	An interquartile range increase in BMI Male, HR 1.27 (1.19-1.36) Female, HR 1.12 (1.00-1.24)	Age, education, smoking, alcohol consumption, total physical activity, postmenopausal hormone therapy, living alone, marital status, and family history of MI, hypertension, high cholesterol, and DM
Hu et al, 2010(Hu et al., 2010b)	3614 (1921M/1693F)/ 59178 (28842M/30336F)	25-74	18.4-year	Male BMI <25, HR 1.00 (reference) BMI 25-29.9, HR 1.25 (1.12-1.39) BMI ≥30, HR 1.99 (1.74-2.27) Female BMI <25, HR 1.00 (reference) BMI 25-29.9, HR 1.33 (1.16-1.51) BMI ≥30, HR 2.06 (1.80-2.37)	Age, study year, education, smoking, alcohol consumption, history of MI, valvular heart disease, DM, SBP, total cholesterol, and physical activity

Table 1 continued

Abdominal obesity					
Ingelsson et al, 2005(Ingelsson et al., 2005c)	104M/1187M	≥70	8.9-year (median)	each 1-SD increase in WC HR 1.36 (1.10-1.69)	DM, prior MI, hypertension, smoking, ECG LVH, and serum total cholesterol
Nicklas et al, 2006(Nicklas et al., 2006)	166 (73M/93F)/ 2435 (1081M/1354F)		6.1-year (median)	each 1-SD increase in WC HR 1.32 (1.12-1.55) each 1-SD increase in WTR HR 1.15 (0.96-1.36)	Age, sex, race, site, education, smoking, chronic obstructive pulmonary disease, inflammation, incident MI, homeostasis model assessment of insulin sensitivity index, DM, and hypertension
Bahrami et al, 2008(Bahrami et al., 2008)	79/6814 (3204M/3610F)	45-84	4-year (median)	WC >102 cm in men, WC >88 cm in women HR 2.06 (1.25-3.41)	Age, gender, hypertension, DM, LVH, Serum cholesterol, and current smoking,
Loehr et al, 2009(Loehr et al., 2009)	1528(825M/703F) /14641(6632M/8009F)	45-65	16-year (median)	each 1-SD increase in WC Male, HR 1.52 (1.43-1.62) Female, HR 1.54 (1.44-1.66) each 1-SD increase in WHR Male, HR 1.50 (1.41-1.60) Female, HR 1.59 (1.46-1.72)	Age, alcohol use, educational level, smoking status, and center

Table 1 continued

Levitan et al, 2009(Levitan et al., 2009a)	1100(718M/382F) /80360(43487M /36873F)	45-79M /48-83F	7-year (median)	An interquartile range increase in WC Male, HR 1.31 (1.21-1.42) Female, HR 1.20 (1.05-1.36) An interquartile range increase in WHR Male, HR 1.08 (1.00-1.17) Female, HR 1.02 (0.93-1.12) An interquartile range increase in WHtR Male, HR 1.28 (1.18-1.39) Female, HR 1.14 (1.00-1.31)	Age, education, smoking, alcohol consumption, total physical activity, postmenopausal hormone therapy, living alone, marital status, and family history of MI, hypertension, high cholesterol, and DM
Hu et al, 2010(Hu et al., 2010b)	3614 (1921M/1693F)/ 59178(28842M/30336F)	25-74	18.4-year	each 1-cm increase in WC Male, HR 1.03 (1.02-1.04) Female, HR 1.04 (1.03-1.05) each 0.1-unit increase in WHR Male, HR 1.48 (1.25-1.75) Female, HR 1.64 (1.31-2.04)	Age, study year, education, smoking, alcohol consumption, history of MI, valvular heart disease, DM, SBP, total cholesterol, physical activity

*The number of subjects are those were finally included in the analyses.

Abbreviations: BMI=body mass index, CHD=coronary heart disease, DM=diabetes mellitus, ECG=Electrocardiograph, MI=myocardial infarction, SBP=systolic blood pressure, WC= waist circumference, WHR=waist-to-hip ratio, LVH=left ventricular hypertrophy, HR=hazard ratio, WTR=waist-to-thigh ratio.

Table 2. Selected findings on the association between physical activity and the risk of heart failure

Author, year	No. of heart failure cases /No. of participants*	Age range (years)	Follow-up	Major findings Hazard ratios (95% CI)	Adjustment factors
He et al, 2001(He et al., 2001)	1382 (741M/641F） /13643(5545M/8098F)	25-74	19-year	Regular exercise, HR 1.00 (reference) Low exercise, Male, HR 1.14 (0.94-1.38) Female, HR 1.31 (1.11-1.54)	Age, race, education level, smoking, regular alcohol consumption, SBP, overweight, hypertension, history of DM, history of valvular heart disease, and history of CHD
Kenchaiah et al, 2009(Kenchaiah et al., 2009)	1109M/21094M	40-84	20.5-year	Vigorous physical activity Low, HR 1.00 (reference) Active ≥1-3 times/mo, HR 0.82 (0.70-0.96)	Age, cigarette smoking, alcohol consumption, parental history of MI, random assignment to aspirin or β-carotene, BMI, the presence or absence of history of hypertension, DM, and hypercholesterolemia

Table 2 continued

Hu et al, 2010(Hu et al., 2010b)	3614(1921M/1693F)/ 59178(28842M/30336F)	25-74	18.4-year	Low exercise, HR 1.00 (reference) Moderate exercise, Male, HR 0.79 (0.68-0.92) Female, HR 0.86 (0.75-0.99) High exercise, Male, HR 0.69 (0.60-0.80) Female, HR 0.68 (0.59-0.78)	Age, study year, education, smoking, alcohol consumption, history of MI, valvular heart disease, DM, SBP, total cholesterol, and BMI

*The number of subjects are those were finally included in the analyses.
Abbreviations: BMI=body mass index, CHD=coronary heart disease, DM=diabetes mellitus, MI=myocardial infarction, SBP=systolic blood pressure.

7,495 participants of the Multifactor Primary Prevention Study,in which the association of coffee consumption with HF were first studied in bivariate analysis and further studied in multiple logistic regression.(Wilhelmsen et al., 2001) Coffee consumption was classified into three categories: 0, 1-4, ≥5cups/day in the bivariate analysis. Result of this analysis indicated that coffee consumption is marginally associated with HF risk. When entered the multiple logistic regression model, coffee consumption was analyzed as a variable of two category (<5 cups/day and ≥5cups/day). Results of this analysis suggested that coffee consumption ≥5cups/day (relative risk = 1.17; 95% confidence interval [CI], 1.05-1.30, compared with coffee consumption <5 cups/day) was an independent predictor of HF.(Wilhelmsen et al., 2001) In a cohort of Swedish men, a prospective cohort of 37,315 men aged 45-79 years old, Ahmed et al.(Ahmed et al., 2009) classified coffee consumption into five categories: <1 cup/day, 2 cups/day, 3 cups/day, 4 cups/day and ≥ 5 cups/day. They did not find a significant association between coffee consumption and HF hospitalization and HF mortality. Furthermore, the authors conducted a 4 degree of freedom likelihood ratio test to exam whether including coffee consumption added information to the model. Result of this likelihood ratio test confirmed that coffee consumption was not a significant predictor of HF events.(Ahmed et al., 2009) Results from the two previous studies were inconsistent.(Ahmed et al., 2009; Wilhelmsen et al., 2001) Also, both studies were conducted in men, and it is unclear whether coffee consumption is an independent risk factor of HF in women. The Finnish population has the highest per capita coffee consumption in the world, at 11.4 kg/year.(World Resources Institute) Research into the potential health effects of coffee in this population is therefore of particular interest.

Lifestyle pattern and HF

The respective influence of lifestyle factors on the risk of HF has been assessed in several studies. However, the joint association of lifestyle factors with the risk of HF remains unclear. There is only one recent cohort study which demonstrated that having a healthy lifestyle had a statistically independent association with a reduced lifetime risk of HF.(Djousse et al., 2009) This study was conducted on male physicians who certainly had higher health consciousness, which limited its generalizability. Further studies are needed in explaining the influence of modifiable lifestyle factors on the risk of HF in other populations. Also, it is unknown that if the joint associations between lifestyle factors and the risk of heart failure in people with underlying hypertension is similar with that in the general population.

CHAPTER 2. OCCUPATIONAL, COMMUTING AND LEISURE-TIME PHYSICAL ACTIVITY IN RELATIONS TO HEART FAILURE AMONG FINNISH MEN AND WOMEN[2]

2.1 Introduction

Heart Failure (HF) has emerged as a scourge throughout the developed and developing regions of the world (Nieminen and Harjola, 2005; Schocken et al., 2008a). According to the American Heart Association, 550,000 new cases occur in the U.S. each year, and more than 5 million Americans have HF (Schocken et al., 2008a). Although there is strong evidence that regular physical activity has a protective effect against coronary heart disease and stroke (Bassuk and Manson, 2005), studies related to regular physical activity and HF are sparse, and the results of these studies are inconsistent (Djousse et al., 2009; He et al., 2001; Kenchaiah et al., 2009). Furthermore, physical activity has always been represented by leisure-time physical activity in studies related to the association between physical activity and HF (Djousse et al., 2009; He et al., 2001; Kenchaiah et al., 2009), whereas the relationship of HF with occupational or commuting physical activity remains unclear. The aim of this study is to examine whether occupational, commuting, or leisure-time physical activity are independently associated with a reduced HF risk, and moreover, how different combinations of physical activity affects the risk.

2.2 Methods

Subjects

Seven independent population surveys were carried out in 6 geographic areas of Finland

[2] This chapter originally appeared as Yujie Wang, Jaakko Tuomilehto, Pekka Jousilahti, Riitta Antikainen, Markku Mähönen, Peter T. Katzmarzyk, and Gang Hu. Occupational, commuting and leisure-time pphysical activity in relation to heart failure among Finnish men and women. Journal of the American College of Cardiology, 56(14), 1140-1148, 2010. Reprinted by permission of Elsevier. http://content.onlinejacc.org/article.aspx?articleid=1143710

in 1972, 1977, 1982, 1987, 1992, 1997 and 2002 (Vartiainen et al., 2000). In 1972 and 1977, a randomly selected sample of 6.6% of the population born between 1913 and 1947 was drawn. Since 1982, the sample was stratified by area, gender and 10-year age group according to the World Health Organization (WHO) Monitoring trends and determinants of Cardiovascular disease (MONICA) protocol (Pajak et al., 1988). The participation rate varied by year from 65% to 88% (Vartiainen et al., 2000). The subjects included in the seven surveys were 25 to 64 years of age, and the 1997 and 2002 surveys also included subjects aged 65 to 74 years. Subjects who participated in more than one survey were included only in the first survey cohort in which they appeared. The total sample size of the seven surveys was 62,013. After excluding 998 subjects with a history of HF at baseline, and 2807 with incomplete data on any required variables, the present analyses include 28,334 men and 29,874 women. The participants provided an informed consent (verbal 1972-1992 and written 1997 and 2002). These surveys were conducted according to the ethical rules of the National Institute for Health and Welfare, and the investigations were performed in accordance with the Declaration of Helsinki.

Assessment of physical activity

Occupational, commuting, and leisure-time physical activity levels were assessed using a self-administered questionnaire only at baseline. A detailed description of the questions has been presented elsewhere (Hu et al., 2004b; Hu et al., 2007a; Hu et al., 2003; Hu et al., 2005b). The questionnaire used for the assessment of physical activity has been successfully used elsewhere and it has shown a high correlation with physical fitness, as measured by maximal oxygen uptake.(Albanes et al., 1990; Andersen et al., 2000) The subjects reported

their occupational physical activity according to the following three categories: (i) ‘low’ was physically very easy, sitting office work, e.g. secretary; (ii) ‘moderate’ was work including standing and walking, e.g. store assistant, light industrial worker; (iii) ‘high’ was work including walking and lifting, or heavy manual labor, e.g. industrial or farm work. Daily commuting (return journey) was categorized into three categories: (i) motorized transportation or no physical work (no walking or cycling); (ii) walking or bicycling 1 to 29 minutes per day; (iii) walking or bicycling more than 30 minutes per day. Self-reported leisure-time physical activity was classified into three categories: (i) ‘low’ was defined as almost completely inactive, such as reading, watching TV, or doing some minor physical activity but not of moderate or high level; (ii) ‘moderate’ was doing some physical activity more than four hours a week, such as walking, cycling, or light gardening, excluding travel to work; (iii) ‘high’ was performing vigorous physical activity more than three hours a week, such as running, jogging, swimming, or heavy gardening, or competitive sports several times a week.

Other assessments

Smoking, socioeconomic factors, alcohol consumption, and medical history were also assessed by using the self-administered questionnaire. Based on the questionnaire data, the participants were classified as never smokers, ex-smokers and current smokers. Current smokers were categorized into those who smoked <20 or ≥20 cigarettes per day. Years of education were divided into birth cohort specific tertiles. Since questions on alcohol consumption were different between the first two surveys (1972 and 1977) and the latter surveys, the participants were categorized into abstainers and alcohol users. Data on the

initiation of antihypertensive drug treatment were obtained from the questionnaire and the records of drug register. Subjects who reported having diabetes on the questionnaire, or who had had a hospital discharge diagnosis of diabetes (including asymptomatic diabetes and known diabetes), or who received the approval of a physician for using diabetes medication (either oral glucose-lowering agents or insulin) before the baseline survey were classified as having history of diabetes at baseline (Hu et al., 2003). Data on the history of myocardial infarction at baseline were obtained from the questionnaire and collected by hospital discharge diagnosis, and the overall sensitivity of the diagnosis of myocardial infarction in the FINNISH Hospital Discharge Register was 83% (Pajunen et al., 2005). Data on the history of valvular heart disease at baseline were collected by hospital discharge register. Data on the history of lung disease (pulmonary emphysema, bronchitis, chronic bronchial catarrh) were collected from the questionnaire.

At the study site, trained research nurses measured height, weight, and blood pressure using a standardized protocol (Pajak et al., 1988). Height was measured without shoes and weight was measured with light clothing. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Blood pressure was measured from the right arm after five minutes of sitting. After blood pressure measurement, a venous blood specimen was taken. Total cholesterol was determined by using Lieberman Burchard method in 1972 and 1977 and by an enzymatic method (CHOD-PAP, Boehringer MANNHEIM, Mannheim, Germany) since 1982. Because the enzymatic method gave 2.4% lower values than the Lieberman Burchard method (based on the double measurements of serum samples during the change of laboratory method), the values measured in 1972 and

1977 were corrected by this percentage. All samples were analyzed in the same central laboratory.

Prospective Follow-up

Follow-up information was obtained from the Finnish Hospital Discharge Register and the National Social Insurance Institution's Register on special reimbursement for HF drugs for non-fatal outcomes and the Finnish Death Register for fatal outcomes by using social security numbers assigned to every citizen of Finland. The International Classification of Diseases (ICD) codes 427.00 and 427.10 (ICD-8), 428, 4029B (hypertensive heart disease with HF) and 4148A-X (ischemic HF with chronic coronary heart disease) (ICD-9), and I 50, I11.0 (hypertensive heart disease with HF), I13.0 and I13.2 (hypertensive heart and renal disease with HF) (ICD-10) were used to identify cases in the above national databases. A HF diagnosis was made by the treating physicians, based on a clinical assessment, X-ray examination and, to various extents, echocardiography. Follow-up of each cohort member continued until the date of the diagnosis of HF obtained from the Hospital Discharge Register, the National Social Insurance Institution's Register or mortality, death from causes other than HF, or December 31, 2006 (Hu et al., 2010a). This diagnosed method has been used in other Scandinavian countries, such as Sweden. The accuracy of the HF cases in the Swedish hospital discharge is found to be over 80% based on the European Society of Cardiology (ESC) definition.(Ingelsson et al., 2005a; Levitan et al., 2009a)

Statistical analyses

Differences in risk factors between groups with different physical activity levels were tested using univariate analysis of variance (ANOVA) after adjustment for age and study

year. Cox proportional hazards regression models were used to analyze the association of physical activity with the risk of HF. Physical activity categories were included in the models as dummy and categorical variables, and the significance of the trend over different categories of physical activity was tested in the same models by giving an ordinal numeric value for each dummy variable. The proportional hazards assumption in the Cox model was assessed with graphical methods, and with models including time-by-covariate interactions (Cox, 1972). In general, all proportionality assumptions were appropriate. The analyses were first carried out adjusting for age and study year, and further for smoking, education, alcohol consumption, history of myocardial infarction, history of valvular heart disease, history of diabetes, history of using anti-hypertensive drugs, history of lung disease, BMI, systolic blood pressure, and total cholesterol, and further for other two types of physical activity. To avoid a potential bias due to severe disease at baseline, additional analyses were carried out excluding the subjects who died during the first two years of follow-up (n=408). Statistical significance was considered to be $P<0.05$. Statistical package SPSS for Windows, version 17.0 (SPSS Inc, Chicago, III), was used for statistical analysis.

2.3 Results

During a mean follow-up of 18.4 years, 1868 men and 1640 women developed HF. General characteristics of the study population by different types of physical activity at baseline are presented in Table 3. Age- and study year-adjusted partial correlations were 0.23 in men ($P<0.001$) and 0.20 in women ($P<0.001$) for occupational and commuting physical activity, -0.08 in men ($P<0.001$) and -0.04 in women ($P<0.001$) for occupational and leisure-time physical activity, and 0.03 in men ($P<0.001$) and 0.06 in women ($P<0.001$) for

commuting and leisure-time physical activity.

Age- and study year-adjusted hazard ratios (HRs) of HF associated with low, moderate and high occupational physical activity were 1.00, 0.75, and 0.74 (P<0.001 for trend) for men, and 1.00, 0.67, and 0.87 (P<0.001 for trend) for women, respectively (Table 4). In multivariable analyses, after further adjustment for other risk factors (smoking, education, alcohol consumption, history of myocardial infarction, history of valvular heart disease, history of diabetes, history of using anti-hypertensive drugs, history of lung disease, BMI, systolic blood pressure, and total cholesterol), and for commuting and leisure-time physical activity, these inverse associations were still statistically significant for men (P=0.005 for trend) and women (P=0.007 for trend).

Daily commuting physical activity on foot or by bicycle was significantly and inversely associated with the risk of HF among men (P<0.001 for trend) and women (P<0.001 for trend) after adjustment for age and study year (Table 5). The inverse relationship remained significant among women (P=0.008 for trend) but not among men (P=0.374 for trend) after further adjustment for other risk factors. Women spending daily 1-29 minutes in walking or cycling to and from work had a significantly reduced risk of HF than women who had no commuting activity after additional adjustment for occupational and leisure-time physical activity.

Age- and study year-adjusted HRs of HF associated with low, moderate and high leisure-time physical activity were 1.00, 0.81, and 0.53 (P<0.001 for trend) in men, and 1.00 0.71, and 0.56 (P<0.001 for trend) in women, respectively (Table 6). These inverse associations weakened to some extent, but remained statistically significant, after further

Table 3. General characteristics of study subjects at baseline*

	Occupational physical activity							
	Men			P for	Women			P for
	Low	Moderate	High	trend	Low	Moderate	High	trend
No. of subjects	11,069	6,032	11,233		13,115	9,266	7,493	
Age at baseline (yrs)	48.5	42.2	43.0	<0.001	46.8	42.4	44.2	<0.001
Body mass index (kg/m^2)	26.5	26.4	26.3	0.003	26.0	25.7	26.6	<0.001
Diastolic blood pressure (mm Hg)	87	87	86	0.002	83	83	84	<0.001
Systolic blood pressure (mm Hg)	143	142	143	<0.001	138	137	140	<0.001
Serum cholesterol (mmol/l)	6.01	6.04	6.19	<0.001	5.96	5.89	6.09	<0.001
Education (yrs)	10.4	10.6	8.3	<0.001	10.3	10.6	9.1	<0.001
Alcohol drinker (%)	66.3	77.1	63.6	<0.001	40.6	43.4	32.0	<0.001
Current smoker (%)	41.8	36.6	43.2	<0.001	19.3	18.7	16.3	<0.001
History of myocardial infarction (%)	5.5	2.8	1.9	<0.001	1.6	0.6	0.4	<0.001

Table 3 continued

History of valvular heart disease (%)	0.1	0.2	0.1	0.36	0.1	0.1	0.0	0.013
History of diabetes (%)	3.3	2.4	1.7	<0.001	2.6	1.4	1.7	<0.001
History of using anti-hypertensive drugs (%)	12.3	9.5	7.9	<0.001	13.6	9.5	9.9	<0.001
History of lung disease (%)	7.5	4.5	5.3	<0.001	5.1	4.6	4.9	0.261

	Commuting physical activity							
	Men			P for	Women			P for
	0	1-29	≥30	trend	0	1-29	≥30	trend
No. of subjects	15,288	8,565	4,481		13,650	9,609	6,615	
Age at baseline (yrs)	46.2	42.2	46.0	<0.001	47.1	42.1	43.9	<0.001
Body mass index (kg/m^2)	26.5	26.3	26.1	<0.001	26.5	25.8	25.6	<0.001
Diastolic blood pressure (mm Hg)	87	87	87	0.63	83	83	83	0.33
Systolic blood pressure (mm Hg)	143	142	142	<0.001	139	137	137	<0.001
Serum cholesterol (mmol/l)	6.10	6.09	6.07	0.22	6.02	5.92	5.94	<0.001

Table 3 continued

Education (yrs)	9.4	10.0	9.6	<0.001	9.6	10.5	10.4	<0.001
Alcohol drinker (%)	65.7	67.5	65.8	0.012	35.0	44.0	41.5	<0.001
Current smoker (%)	43.5	38.1	39.6	<0.001	18.3	19.0	17.7	0.093
History of myocardial infarction (%)	4.6	2.2	2.1	<0.001	1.5	0.6	0.5	<0.001
History of valvular heart disease (%)	0.1	0.2	0.1	0.46	0.1	0.0	0.1	0.049
History of diabetes (%)	2.7	2.1	2.5	0.009	2.5	1.6	1.2	<0.001
History of using anti-hypertensive drugs (%)	10.9	9.2	8.7	<0.001	13.1	10.3	9.5	<0.001
History of lung disease (%)	6.9	4.9	4.9	<0.001	5.1	4.6	4.9	0.158

	Leisure-time physical activity						
	Men				Women		
	Low	Moderate	High		Low	Moderate	High	
No. of subjects	7,849	14,761	5,724		10,564	15,032	4,278	
Age at baseline (yrs)	45.5	46.3	41.0	<0.001	45.7	45.2	41.3	<0.001

Table 3 continued

Body mass index (kg/m^2)	26.7	26.5	25.7	<0.001	26.9	25.8	25.0	<0.001
Diastolic blood pressure (mm Hg)	87	87	85	<0.001	84	83	82	<0.001
Systolic blood pressure (mm Hg)	143	143	141	<0.001	139	138	136	<0.001
Serum cholesterol (mmol/l)	6.15	6.14	5.88	<0.001	6.01	5.96	5.90	<0.001
Education (yrs)	9.1	9.5	10.6	<0.001	9.7	10.2	10.7	<0.001
Alcohol drinker (%)	63.1	66.8	69.3	<0.001	36.5	39.8	44.6	<0.001
Current smoker (%)	50.0	41.8	27.8	<0.001	21.6	17.8	12.4	<0.001
History of myocardial infarction (%)	3.9	3.7	2.5	<0.001	1.4	0.9	0.5	<0.001
History of valvular heart disease (%)	0.1	0.2	0.1	0.060	0.1	0.1	0.1	0.74
History of diabetes (%)	3.2	2.3	1.8	<0.001	2.3	1.9	1.1	<0.001
History of using anti-hypertensive drugs (%)	10.7	10.4	7.7	<0.001	13.1	11.0	8.1	<0.001
History of lung disease (%)	7.7	5.6	4.6	<0.001	5.7	4.6	3.9	<0.001

*Baseline characteristics represent mean or percentage; adjusted for age and study year.

Table 4. Hazard ratios of heart failure according to different levels of occupational physical activity

	Occupational physical activity			P for trend
	Low	Moderate	High	
Men	11,069	6,032	11,233	
No. of incidence case	777	340	751	
Person-yrs	160,376	117,247	225,292	
Age and study years adjusted HR (95% CI)	1.00	0.75 (0.66-0.85)	0.74 (0.67-0.82)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	0.88 (0.77-1.01)	0.84 (0.75-0.94)	0.006
Multivariable adjustment HR (95% CI)†	1.00	0.90 (0.78-1.03)	0.83 (0.73-0.93)	0.005
Women	13,115	9,266	7,493	
No. of incidence case	759	358	523	
Person-yrs	216,737	189,921	159,959	
Age and study years adjusted HR (95% CI)	1.00	0.67 (0.59-0.76)	0.87 (0.78-0.97)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	0.77 (0.67-0.87)	0.90 (0.80-1.01)	<0.001

Table 4 continued

Multivariable adjustment HR (95% CI)†	1.00	0.80 (0.70-0.92)	0.92 (0.82-1.05)	0.007
Men and women combined‡	24,184	15,298	18,726	
No. of incidence case	1,536	698	1,274	
Person-yrs	377,113	307,168	385,251	
Age and study years adjusted HR (95% CI)	1.00	0.70 (0.64-0.77)	0.79 (0.74-0.85)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	0.82 (0.74-0.90)	0.86 (0.79-0.93)	<0.001
Multivariable adjustment HR (95% CI)†	1.00	0.85 (0.77-0.93)	0.87 (0.80-0.94)	<0.001

HR = hazard ratio; CI = confidence interval.

*Adjusted for age, study year, education, smoking, alcohol consumption, history of myocardial infarction, history of valvular heart disease, history of diabetes, systolic blood pressure, total cholesterol, history of using anti-hypertension drugs, history of lung disease and BMI.

†Adjusted for age, study year, education, smoking, alcohol consumption, history of myocardial infarction, history of valvular heart disease, history of diabetes, systolic blood pressure, total cholesterol, history of using anti-hypertensive drugs, history of lung disease, BMI, and other two types of physical activity.

‡Adjusted also for sex.

Table 5. Hazard ratios of heart failure according to different levels of commuting physical activity

	Walking or cycling to and from work (minutes/day)			P for trend
	0	1-29	≥30	
Men	15,288	8,565	4,481	
No. of incidence case	984	499	385	
Person-yrs	243,541	167,513	91,861	
Age and study years adjusted HR (95% CI)	1.00	0.83 (0.74-0.92)	0.81 (0.72-0.91)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	0.96 (0.86-1.07)	0.92 (0.81-1.04)	0.374
Multivariable adjustment HR (95% CI)†	1.00	1.01 (0.90-1.13)	0.99 (0.87-1.12)	0.954
Women	13,650	9,609	6,615	
No. of incidence case	959	351	330	
Person-yrs	237,004	192,706	136,906	
Age and study years adjusted HR (95% CI)	1.00	0.73 (0.64-0.82)	0.76 (0.67-0.86)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	0.83 (0.73-0.94)	0.89 (0.78-1.01)	0.008

Table 5 continued

Multivariable adjustment HR (95% CI)†	1.00	0.87 (0.76-0.99)	0.94 (0.82-1.07)	0.108
Men and women combined‡	28,938	18,174	11, 096	
No. of incidence case	1,943	850	715	
Person-yrs	480,545	360,220	228,767	
Age and study years adjusted HR (95% CI)	1.00	0.77 (0.71-0.83)	0.76 (0.70-0.83)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	0.88 (0.81-0.96)	0.88 (0.80-0.96)	0.001
Multivariable adjustment HR (95% CI)†	1.00	0.93 (0.85-1.01)	0.93 (0.85-1.02)	0.159

HR = hazard ratio; CI = confidence interval.

*Adjusted for age, study year, education, smoking, alcohol consumption, history of myocardial infarction, history of valvular heart disease, history of diabetes, systolic blood pressure, total cholesterol, history of using anti-hypertension drugs, history of lung disease and BMI.

†Adjusted for age, study year, education, smoking, alcohol consumption, history of myocardial infarction, history of valvular heart disease, history of diabetes, systolic blood pressure, total cholesterol, history of using anti-hypertensive drugs, history of lung disease, BMI, and other two types of physical activity.

‡Adjusted also for sex.

Table 6. Hazard ratios of heart failure according to different levels of leisure time physical activity

	Leisure time physical activity			P for trend
	Low	Moderate	High	
Men	7,849	14,761	5,724	
No. of incidence case	707	995	166	
Person-yrs	140,606	260,215	102,094	
Age and study years adjusted HR (95% CI)	1.00	0.81 (0.73-0.88)	0.53 (0.45-0.62)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	0.84 (0.76-0.93)	0.66 (0.55-0.79)	<0.001
Multivariable adjustment HR (95% CI)†	1.00	0.83 (0.76-0.92)	0.65 (0.54-0.77)	<0.001
Women	10,564	15,032	4,278	
No. of incidence case	940	608	92	
Person-yrs	219,722	273,837	73,058	
Age and study years adjusted HR (95% CI)	1.00	0.71 (0.65-0.79)	0.56 (0.46-0.69)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	0.83 (0.74-0.92)	0.74 (0.59-0.92)	<0.001

Table 6 continued

Multivariable adjustment HR (95% CI)†	1.00	0.84 (0.75-0.93)	0.75 (0.60-0.94)	0.001
Men and women combined‡	18,413	29,793	10,002	
No. of incidence case	1,647	1,603	258	
Person-yrs	360,328	534,052	175,151	
Age and study years adjusted HR (95% CI)	1.00	0.75 (0.70-0.81)	0.54 (0.48-0.61)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	0.83 (0.77-0.89)	0.69 (0.60-0.79)	<0.001
Multivariable adjustment HR (95% CI)†	1.00	0.83 (0.77-0.89)	0.69 (0.60-0.79)	<0.001

HR = hazard ratio; CI = confidence interval.

*Adjusted for age, study year, education, smoking, alcohol consumption, history of myocardial infarction, history of valvular heart disease, history of diabetes, systolic blood pressure, total cholesterol, history of using anti-hypertension drugs, history of lung disease and BMI.

†Adjusted for age, study year, education, smoking, alcohol consumption, history of myocardial infarction, history of valvular heart disease, history of diabetes, systolic blood pressure, total cholesterol, history of using anti-hypertensive drugs, history of lung disease, BMI, and other two types of physical activity.

‡Adjusted also for sex.

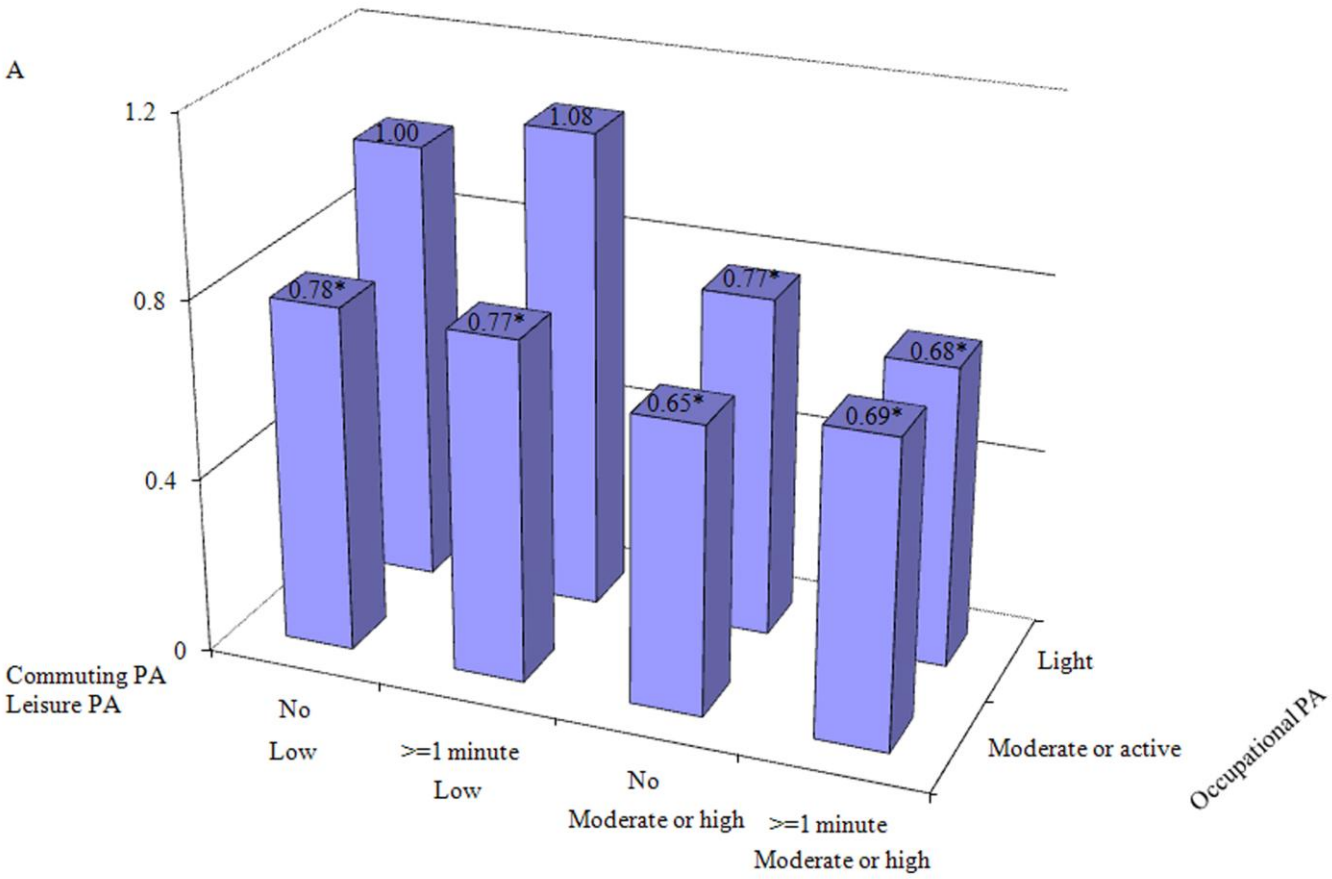
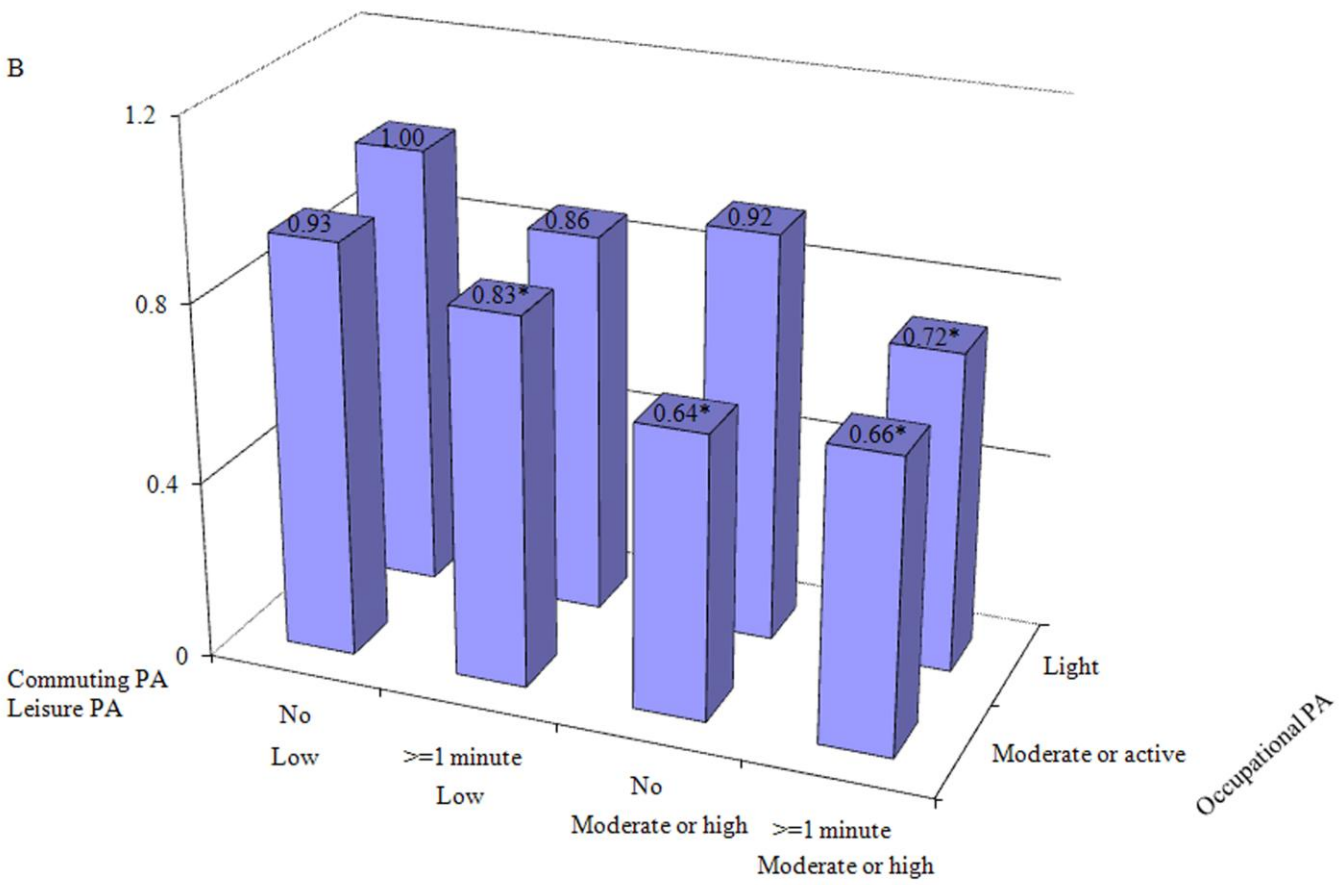


Figure 1. Hazard rations of heart failure according to joint categories of occupational, commuting andleisure-time physical activity among men (A) and women (B).

Adjusted for age, study year, education, smoking, alcohol consumption, history of myocardial infarction, history of valvular heart disease, history of diabetes, history of using anti-hypertensive drugs, history of lung disease BMI, systolic blood pressure, and total cholesterol. *p<0.05


B
1.2
0.8
0.4
0
0.93
1.00
0.83*
0.86
0.64*
0.92
0.66*
0.72*
Commuting PA
Leisure PA
No
Low
>=1 minute
Low
No
Moderate or high
>=1 minute
Moderate or high
Light
Moderate or active
Occupational PA

adjustment for other risk factors and occupational and commuting physical activity (both P<0.001 for trend).

The joint effects of different types of physical activity on the risk of HF are presented in Figure 1. We dichotomized the level of occupational and leisure-time physical activity at low versus moderate to high and the level of commuting physical activity as any versus none. Among men, both moderate or high levels of leisure-time physical activity and moderate or high levels of occupational physical activity had inverse associations with HF risk. The combination of any two types of physical activity or the made this favorable effect even bigger. Among women, none of the three types of physical activity alone is significantly associated with a reduced risk of HF. However, the risk of HF significantly reduced among women with more than one type of physical activity. After adjustment for age, study year, and other risk factors, men with high levels of all three types of physical activity had a 31% lower risk of HF as compared with the least active men. In women, the risk reduction was 34%.

Exclusion of the participants who died during the first two years of follow-up did not appreciably change the results above.

2.4 Discussion

Moderate and high levels of occupational or leisure-time physical activity are associated with a reduced risk of HF in both sexes. Commuting activity was inversely associated with HF risk among women before adjustment for occupational and leisure time physical activity. A simultaneous engagement in two or three types of physical activity showed a slightly stronger protective effect than participation in only one type of physical activity.

To the best of our knowledge, only three studies have assessed the association between physical activity and the risk of HF (Djousse et al., 2009; He et al., 2001; Hu et al., 2010a; Kenchaiah et al., 2009), and only one of them included both men and women (He et al., 2001). Moreover, the results of the three studies were inconsistent.(Djousse et al., 2009; He et al., 2001; Hu et al., 2010a; Kenchaiah et al., 2009) Physical activity was found to be a protective factor against HF among men in the Physicians' Health Study.(Djousse et al., 2009; Kenchaiah et al., 2009) On the other hand, in the First National Health and Nutrition Examination Survey, the significant inverse association between leisure-time physical activity and HF risk was found only in women but not in men(He et al., 2001). In the present study, for the first time, moderate or high physical activity levels were found to be associated with a decreased risk of HF in both men and women.

All of the previous studies focused on leisure-time activity. (Djousse et al., 2009; He et al., 2001; Kenchaiah et al., 2009) However, the present study shows for the first time that moderate or high occupational physical activity also has the same protective effect on the risk of HF as leisure-time physical activity, especially in men. If this finding represents a causal relation, this approach is highly relevant to the improvement of health and longevity among working-aged people, because the increase in computerization and mechanization during the last decades has resulted in ever-increasing numbers of people being sedentary for most of their working time. Occupational physical activity has been largely ignored in epidemiological surveys. The National Institutes of Health Consensus Development Conference on Physical Activity and Cardiovascular Health concluded that intermittent or shorter bouts of physical activity (at least 10 minutes), including occupational and

non-occupational activity and tasks of daily living, have similar HF preventive effects and other health benefits if performed at a level of moderate intensity (such as brisk walking, cycling, swimming, home repair, and yard work) with an accumulated duration of at least 30 minutes per day (NIH Consensus Development Panel on Physical Activity and Cardiovascular Health, 1996).

The present study is also the first study which observed an association between commuting physical activity and the risk of HF. We observed the significant inverse association between active commuting with the risk of HF events in women before adjustment for occupational and leisure time physical activity. Although we did not establish a significant association between the risk of HF and commuting physical activity alone in both men and women, we confirmed that an individual with moderate or high leisure-time or occupational physical activity experienced further reduced risk of HF, when he was also engaged in commuting physical activity. This is an important finding because daily active commuting is a major source of total physical activity in some populations, can be implemented virtually everywhere, and is inexpensive. For example, in urban China more than 90% of people walk or cycle to and from work daily (Hu et al., 2002) . In our study, 54% of women and 46% of men reported walking or cycling to work daily, and 22% of women and 16% of men reported more than a half hour walking or cycling to work daily. Several studies have shown that regular walking or cycling to and from work is related to lower levels of cardiovascular risk factors (Hu et al., 2001; Hu et al., 2002; Hu et al., 2003), as well as a reduced risk of type 2 diabetes (Hu et al., 2003), stroke (Hu et al., 2005b), and CHD incidences (Hu et al., 2007a), and mortality in general populations and patients with

diabetes (Andersen et al., 2000; Hu et al., 2004b). In many Western studies, commuting physical activity was indirectly measured by asking for the frequency and duration of walking or cycling. Our results emphasize commuting as a separate component of physical activity to prevent HF in women**.**

The differences between the results of the present study and the previous studies may be partially explained by the relatively larger sample size of both men and women; the inclusion of physical activity during occupation, commuting, and leisure time; more incident HF cases; and different adjustment procedures in the present study. When assessing the joint effects of different types of physical activity, we observed a slightly higher risk of HF in those who participated in three types of physical activity. By our classification, it was possible that the level of the three types of physical activity in which those participants engaged were moderate levels of physical activity, while it is also possible for participants to take part in two types of physical activity the level of which were high levels of physical activity. This may partly account for the observed trend. Moreover, the present study indicated that the lowest hazard ratios occurred in women who did moderate occupational and commuting physical activity. Older age and higher levels of CVD risk factors in women with high occupational physical activity compared with women with moderate occupational physical activity may partly account for the observed trend although we took these CVD risk factors into account in the multivariable analyses. Except for older age, other possible reasons for the loss of dose effect between commuting physical activity and HF risk among women in our study was unknown.

The protective effect of physical activity to HF may be partly mediated by its effect on

other risk factors for HF. Physical activity has a favorable effect on blood pressure, lipid profile, insulin sensitivity, body weight, blood coagulation, and fibrinolysis (Gris et al., 1990; Hu et al., 2004a; Hu et al., 2007a; Hu et al., 2001; Hu et al., 2002; Mayer-Davis et al., 1998), and it is also contributed to a decreased risk of developing hypertension, type 2 diabetes, the metabolic syndrome and CHD (Hu et al., 2004a; Hu et al., 2007a; Hu et al., 2003; Hu et al., 2007c; Laaksonen et al., 2002; Tuomilehto et al., 2001). In our study population, it has been previously shown that moderate or high levels of occupational or leisure-time physical activity were associated with a reduced risk of CHD, and daily walking or cycling to and from work was associated with a decreased risk of CHD among women (Hu et al., 2007a; Hu et al., 2007c). The current findings on the relationship between physical activity and the risk of HF are similar with the previous findings about the association between physical activity and the risk of CHD. In the present study, the inverse association between physical activity and the risk of HF remained after adjusting for major HF risk factors. However, given the temporal lag between the assessment of physical activity at baseline and the measurement of the outcome, it is not possible to determine the pathways by which physical activity resulted in lower risk of HF.

There are several strengths and limitations in our study. First, a major strength of the study is the large number of both men and women from a homogeneous population who participated in the study. Second, the mean follow-up time was sufficiently long to ascertain a large number of HF endpoint events. Not only leisure-time physical activity, but also occupational and commuting physical activities were included in the analysis. Finally, we also carried out additional analyses excluding the subjects who died during the first two

years of follow-up to avoid a potential bias due to a severe disease at baseline. A limitation of our study is the self-report of physical activity, and that physical activity was recorded only once at baseline. Although no specific assessment of repeatability or validity of our questionnaire for physical activity has been carried out, similar questionnaires have been used in a large number of studies in Finland and other Nordic countries (Andersen et al., 2000; Hu et al., 2004b; Hu et al., 2007a; Hu et al., 2003; Hu et al., 2005b) where the patterns of physical activity are relatively similar. The method has been working in a large number of studies that can be considered as a validation in practice.(Albanes et al., 1990; Andersen et al., 2000) We have no data on possible changes in physical activity during the follow-up. Misclassification, particularly over-reporting of the amount of physical activity at baseline and changes in the activity during the follow-up probably underestimated the association between physical activity and the outcome. Because our data allowed for only a dichotomized measure of alcohol consumption in the whole sample, we may not be able to fully control for the effect of this variable on the risk of HF. In order to evaluate the impact of this shortcoming we performed separate subgroup analyses (surveys of 1982, 1987, 1992, 1997 and 2002) in the multivariable-adjusted model of a dichotomized measure of alcohol consumption compared with another multivariable-adjusted model of 4 categories of alcohol consumption. In general, the associations between different types of physical activity and HF risk were not influenced substantially or systematically. Ascertainment of HF status was based on the National Hospital Discharge Registry, the National Social Insurance Institution's Register on special reimbursement for HF drugs, and Causes of Death Register. This diagnosis method has been used in other Scandinavian countries, such as Finland and

Sweden (Hu et al., 2010a; Ingelsson et al., 2005a; Levitan et al., 2009a; Wang et al., 2009). The accuracy of the HF cases in the Swedish hospital discharge is found to be over 80% based on the ESC definition (Ingelsson et al., 2005a; Levitan et al., 2009a). Although accuracy of clinical HF diagnosis in our cohort is likely to be high, some diagnostic errors are inevitable. However, the misdiagnosis is most likely to be independent of the exposure status and therefore tends to attenuate the underlying associations rather than cause spurious associations. We cannot completely either exclude the effects of residual confounding due to measurement error in the assessment of confounding factors, or some unmeasured factors, such as other chronic diseases (e.g., peripheral vascular disease, renal disease, and anemia), the extent or severity of the prior MI, ischemic heart disease symptom burden, and some dietary factors.

In conclusion, our study confirms that moderate or high levels of occupational or leisure-time physical activity have negative association with the risk of HF among men and women. Active commuting had a significant inverse association with the risk of HF events in women before adjustment for occupational and leisure time physical activity.

CHAPTER 3. COFFEE CONSUMPTION AND THE RISK OF HEART FAILURE IN FINNISH MEN AND WOMEN[3]

3.1 Introduction

Heart failure (HF) has emerged as a major and growing health problem both in the developed and developing regions of the world.(Schocken et al., 2008a) Although use of medication has reduced re-hospitalization rates and mortality from HF, HF is still the leading cause of hospitalization for older people in the United States,(Kozak et al., 2006) and mortality among HF patients has remained substantial, with approximately one quarter of patients dying within one year and half within five years of diagnosis. Therefore, the prevention of HF through lifestyle approaches is an important public health consideration.

Coffee is one of the most widely consumed beverages in the world.(Popkin et al., 2006) It has been suggested that coffee consumption may be associated with the risk of coronary heart disease (CHD),(Wu et al., 2009) hypertension,(Noordzij et al., 2005) and type 2 diabetes.(Tuomilehto et al., 2004; van Dam and Hu, 2005) Two prospective studies have previously investigated the association between coffee consumption and HF risk among Swedish men.(Ahmed et al., 2009; Wilhelmsen et al., 2001) One showed that coffee consumption increased the risk of HF,(Wilhelmsen et al., 2001) while the other found an null association between coffee consumption and the risk of HF.(Ahmed et al., 2009) Also, both studies were conducted in men, and it is unclear whether coffee consumption is an independent risk factor of HF in women. The Finnish population has the highest per capita coffee consumption in the world, at 11.4 kg/year.(World Resources Institute) Therefore, the aim of

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this study was to examine the association of coffee consumption with the risk of HF in a large prospective cohort of Finnish men and women.

3.2 Methods

Subjects

Seven independent cross-sectional population surveys were carried out in six geographic areas of Finland in 1972, 1977, 1982, 1987, 1992, 1997 and 2002.(Vartiainen et al., 2000) In 1972 and 1977, a randomly selected sample making up 6.6% of the population born between 1913 and 1947 was drawn. Since 1982, the sample was stratified by area, gender and 10-year age group according to the World Health Organization (WHO) MONICA (MONItoring trends and determinants of CArdiovascular disease) protocol.(Pajak et al., 1988) The participation rate varied by year from 65% to 88%.(Vartiainen et al., 2000) The subjects included in the seven surveys were 25 to 64 years of age, and the 1997 and 2002 surveys also included subjects aged 65 to 74 years. Subjects who participated in more than one survey were included only in the first survey cohort. The total sample size of the seven surveys was 62,013. After excluding 998 subjects with a history of HF at baseline, and 1525 with incomplete data on any required variables, the present analyses include 28,837 men and 30,653 women. The participants provided an informed consent (verbal from 1972 to 1992 and written 1997 and 2002). These surveys were conducted according to the ethical rules of the National Public Health Institute, and the investigations were performed in accordance with the Declaration of Helsinki.

Baseline measurements

A self-administered questionnaire was mailed to the participants to be completed at home and returned to the survey site. The questionnaire included questions on medical history, socioeconomic factors, physical activity, smoking habits, and alcohol consumption. Education level, measured as the total number of school years, was divided into birth cohort specific tertiles. Physical activity included occupational, commuting, and leisure time physical activity. A detailed description of the questions is presented elsewhere.(Hu et al., 2003) The subjects reported their occupational physical activity according to the following three categories: light, moderate and active. The daily commuting return journey to work was grouped into three categories: (i) using motorized transportation, or not working outside home (0 minutes of walking or cycling); (ii) walking or bicycling 1 to 29 minutes; (iii) walking or bicycling for more than 30 minutes. Self-reported leisure time physical activity was classified into three categories: low, moderate and high. Since we found that moderate and high occupational, commuting or leisure time physical activity independently and significantly reduces risk of HF (data not shown), the groups were merged into three categories: (i) low was defined as subjects who reported light levels of occupational, commuting (<1 minute) and leisure time physical activity; (ii) moderate was defined as subjects who reported only one of the all three types of moderate to high physical activity; (iii) high was defined as subjects who reported two or three types of moderate to high physical activity. Participants were also classified as never, ex- and current-smokers based on their responses to the questionnaire. Current smokers were categorized into those participants who smoked <20, or ≥20 cigarettes per day. Since questions on alcohol consumption were different between the first 2 surveys

(1972 and 1977) and the latter surveys, the participants were categorized into abstainers and alcohol users. Data on the history of myocardial infarction or diabetes at baseline were obtained from the questionnaire and collected by hospital discharge or drug register. Data on the history of valvular heart disease at baseline were collected from the national hospital discharge register by record linkage.

The participants were asked, "How many cups of coffee or tea do you drink daily (1 cup of coffee equals to 1 dL; one cup of tea equal to 2 dL)?"(Tuomilehto et al., 2004) Based on the validation study of the dietary questionnaire carried out in subgroups of the study population,(Paalanen et al., 2006) the correlations between the dietary questionnaire and food records for the amount of coffee consumed were 0.89 in men and 0.85 in women. Coffee consumption was categorized into six categories: 0 cup, 1-2 cups, 3-4 cups, 5-6 cups, 7-9 cups and ≥10 cups per day. As only a few people drank tea, tea consumption was categorized into three categories: none, 1-2 cups, and ≥3 cups.

At the survey site, specially trained research nurses measured participants' height and weight by using the standardized WHO MONICA protocol.(Pajak et al., 1988) Height and weight were measured without shoes and with light clothing. The measurements of height were rounded to the nearest centimeter and weight to nearest 100 grams.(Pajak et al., 1988) Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Blood pressure was measured from the right arm after five minutes of sitting using a mercury sphygmomanometer in each survey. After blood pressure measurement, a venous blood specimen was taken. Total cholesterol was determined by using Lieberman Burchard method in 1972 and 1977 and by an enzymatic method (CHOD-PAP, Boehringer

MANNHEIM, Mannheim, Germany) since 1982. Because the enzymatic method gave 2.4% lower values than the Lieberman-Burchard method, the values measured in 1972 and 1977 were corrected by this percentage.(Sundvall et al., 2007) All samples were analyzed in the same central laboratory at the National Public Health Institute.

Prospective follow-up

Follow-up information was from the Finnish Hospital Discharge Register and the National Social Insurance Institution's Register on special reimbursement for HF drugs for non-fatal outcomes and the Finnish Death Register for fatal outcomes by record linkage using the personal identification numbers assigned to every citizen of Finland. The International Classification of Diseases (ICD) codes 427.00 and 427.10 (ICD-8), 428, 4029B (hypertensive heart disease with HF) and 4148A-X (ischemic HF with chronic CHD) (ICD-9), and I 50, I11.0 (hypertensive heart disease with HF), I13.0 and I13.2 (hypertensive heart and renal disease with HF) (ICD-10) were used to identify HF cases in the above-mentioned national databases. A HF diagnosis was made by the treating physicians, based on a clinical assessment, X-ray examination and, to various extents echocardiography. Follow-up of each cohort member continued until the date of the diagnosis of HF from Hospital Discharge Register, the National Social Insurance Institution's Register or mortality, death from causes other than HF, or December 31, 2007. This method to ascertain HF cases in prospective epidemiological studies has been used in other Scandinavian countries, such as Sweden. The accuracy of the HF cases in the Swedish hospital discharge is found to be over 80% compared with the European Society of Cardiology (ESC) definition of HF.(Ingelsson et al., 2005a)

Statistical analyses

Differences in risk factors at baseline based on different levels of coffee consumption were tested using General Linear Model after adjustment for age and study year. Cox proportional hazards regression models were used to analyze the association of coffee consumption with the risk of HF. Coffee consumption categories were included in the models as dummy and categorical variables, and the significance of the trend over different categories of coffee consumption was tested in the same models by giving an ordinal numeric value for each dummy variable. The proportional hazards assumption in the Cox model was assessed with graphical methods, and with models including time-by-covariate interactions.(Cox, 1972) In general, all proportionality assumptions were appropriate. The analyses were first carried out adjusting for age and study year, and further adjusting for smoking, education, alcohol consumption, tea consumption, physical activity, BMI, systolic blood pressure, history of myocardial infarction, history of valvular heart disease, history of diabetes, and total cholesterol. To avoid a potential bias due to severe disease at baseline, additional analyses were carried out excluding the subjects who died during the first two years of follow-up (n=483). Statistical significance was considered to be $P<0.05$. Statistical package SPSS for Windows, version 17.0 (SPSS Inc, Chicago, III), was used for statistical analysis.

3.3 Results

During a mean follow-up of 19.2 years, 2020 men and 1807 women developed HF. General characteristics of the study population at baseline are presented by levels of coffee consumption in Table 7. After adjustment for age and study year, coffee consumption had a

Table 7. Baseline characteristics among men and women by volume of coffee consumption*

Characteristics	Daily coffee consumption, cups						P value for trend
	0	1-2	3-4	5-6	7-9	≥10	
Men							
Participants, n	1887	3510	7042	8916	4127	3355	
Age, y	43.6(0.3)	45.7(0.2)	45.8(0.1)	45.6(0.1)	44.3(0.2)	43.0(0.2)	<0.001
BMI, kg/m^2	26.0(0.1)	26.3(0.1)	26.4(0.0)	26.5(0.0)	26.4(0.0)	26.6(0.1)	<0.001
Systolic blood pressure, mmHg	141(0.1)	143(0.3)	143(0.2)	142(0.2)	142(0.3)	142(0.3)	<0.001
Diastolic blood pressure, mmHg	86(0.3)	88(0.2)	87(0.1)	87(0.1)	86(0.2)	86(0.2)	<0.001
Total cholesterol, mg/dL	224(1.0)	229(0.7)	234(0.5)	238(0.5)	241(0.7)	243 (0.8)	<0.001
Education, y	10.2(0.1)	10.3(0.1)	10.0(0.0)	9.3 (0.0)	9.0(0.1)	8.8(0.1)	<0.001
Low physical activity, %	8.9	8.1	7.2	7.6	7.3	10.0	<0.001
Tea drinker, %	65.0	63.3	41.1	24.7	14.4	11.5	<0.001
Alcohol drinker, %	55.2	72.5	69.1	66.6	63.9	60.0	<0.001

Table 7 continued

Current smoker, %	22.7	29.3	33.7	42.8	50.4	64.6	<0.001
History of myocardial infarction, %	3.2	3.7	4.2	3.7	2.4	2.8	<0.001
History of diabetes, %	2.1	3.0	2.3	2.3	2.4	2.6	0.176
History of valvular heart disease, %	0.2	0.2	0.2	0.1	0.0	0.1	0.341
Women							
Participants, n	2015	4348	9777	9775	3287	1451	
Age, y	40.0(0.3)	44.5(0.2)	45.8(0.1)	45.9(0.1)	44.3(0.2)	43.2(0.3)	<0.001
BMI, kg/m^2	25.8(0.1)	25.7(0.1)	25.9(0.0)	26.3(0.0)	26.6 (0.1)	26.9(0.1)	<0.001
Systolic blood pressure, mmHg	139(0.4)	138(0.3)	138(0.2)	139(0.2)	138(0.3)	138 (0.5)	0.200
Diastolic blood pressure, mmHg	82(0.2)	83(0.2)	83(0.1)	83 (0.1)	83(0.2)	82(0.3)	<0.001
Total cholesterol, mg/dL	229(1.0)	228(0.7)	230(0.4)	233(0.4)	235 (0.8)	233(1.1)	<0.001
Education, y	10.5(0.1)	10.7(0.0)	10.3(0.0)	9.7(0.0)	9.3(0.1)	9.2(0.1)	<0.001
Low physical activity, %	13.6	10.8	9.1	8.5	9.1	11.8	<0.001

Table 7 continued

Tea drinker, %	69.0	65.8	43.8	25.4	14.7	12.5	<0.001
Alcohol drinker, %	29.6	43.0	41.0	37.8	36.6	36.8	<0.001
Current smoker, %	5.3	10.7	15.2	20.9	25.1	43.4	<0.001
History of myocardial infarction, %	1.5	1.4	0.9	0.8	0.6	1.1	0.001
History of diabetes, %	2.3	2.2	1.8	1.7	2.1	1.7	0.267
History of valvular heart disease, %	0.1	0.1	0.1	0.1	0.0	0.0	0.377

*All data, except age, adjusted for age and study year.
*Values represent mean (SE) or percentage.

Table 8. Hazard ratio for heart failure by categories of coffee consumption

	Daily coffee consumption, cups						P value
	0	1-2	3-4	5-6	7-9	≥10	for trend
Men							
No. of cases	113	185	438	691	338	255	
Person-years	32097	61573	126507	169558	82149	61938	
Adjustment for age and study year	1.00	0.97 (0.76-1.24)	1.05 (0.85-1.30)	1.12 (0.91-1.38)	1.17 (0.94-1.47)	1.41 (1.13-1.78)	0.001
Multivariate adjustment*	1.00	0.91 (0.71-1.16)	0.88 (0.70-1.10)	0.91 (0.73-1.13)	0.96 (0.76-1.22)	1.02 (0.80-1.30)	0.485
Women							
No. of cases	84	149	514	681	257	122	
Person-years	31833	74339	184786	212511	75168	29983	
Adjustment for age and study year	1.00	0.73 (0.56-0.97)	0.76 (0.60-0.97)	0.74 (0.58-0.93)	0.88 (0.68-1.14)	1.12 (0.85-1.50)	<0.001
Multivariate adjustment*	1.00	0.73 (0.56-0.97)	0.77 (0.60-0.98)	0.68 (0.53-0.88)	0.80 (0.61-1.04)	0.88 (0.65-1.19)	0.007

*Adjusted for age, study year, education, cigarette smoking (never, past, and current smoking of 1-19 or ≥20 cigarettes/d), alcohol consumption (yes and no), physical activity, BMI, systolic blood pressure, total cholesterol, history of myocardial infarction, diabetes, valvular heart disease, and tea consumption.

Table 9. Hazard ratio for heart failure by categories of tea consumption

	Daily tea consumption, cups			P value for trend
	0	1-2	≥3	
Men				
No. of participants	19,312	6,888	2,637	
No. of cases	1, 472	379	169	
Person-years	361,420	122,015	50,388	
Adjustment for age and study year	1.00	0.85 (0.76-0.95)	0.80 (0.68-0.95)	0.002
Multivariate adjustment*	1.00	0.96 (0.85-1.08)	0.96 (0.81-1.15)	0.741
Women				
No. of participants	18,969	9,394	2,290	
No. of cases	1, 268	413	126	
Person-years	389,614	175,855	43,152	
Adjustment for age and study year	1.00	0.84 (0.76-0.94)	0.99 (0.83-1.19)	0.011
Multivariate adjustment*	1.00	0.90 (0.80-1.01)	0.98 (0.81-1.20)	0.208

* Adjusted for age, study year, education, cigarette smoking (never, past, and current smoking of 1-19 or ≥20 cigarettes/d), alcohol consumption (yes and no), physical activity, BMI, systolic blood pressure, total cholesterol, history of myocardial infarction, diabetes, valvular heart disease, and coffee consumption.

direct association with BMI level and current smoking, and an inverse association with education level and tea consumption.

In age and study year-adjusted analysis, we found a positive association between coffee consumption and the risk of HF for men (Table 8); however, when we further adjusted for other risk factors (BMI, smoking, education, alcohol consumption, tea consumption, physical activity, systolic blood pressure, history of myocardial infarction, history of valvular hear disease, history of diabetes, and total cholesterol), the positive association in men disappeared, which suggests that the age and study year-adjusted results were strongly confounded by other risk factors for HF. In women, a significant inverse association between low-to-moderate coffee consumption (1-6 cups/day) and the risk of HF was found in age and study year-adjusted analysis. Additional adjustment for other risk factors did not appreciably alter the results. The pooled multivariable-adjusted hazard ratios **(**HRs) across categories of coffee consumption were 1.00, 0.83 (95% confidence interval [CI] 0.69-1.00), 0.85 (95% CI 0.72-1.00), 0.81 (95% CI 0.69-0.96), 0.90 (95% CI 0.76-1.08), and 0.98 (95% CI 0.81-1.18) (P_{trend}=0.009).

In age and study year-adjusted analysis, we found a negative association between tea consumption and the risk of HF for men and women (P_{trend}=0.002 for men and P_{trend}=0.011 for women) (Table 9). After further adjustment for other risk factors, these inverse associations were no longer significant (all P_{trend}>0.2).

Stratification by age, smoking status, alcohol consumption, history of type 2 diabetes mellitus, and BMI gave similar results.

Exclusion of the participants who died during the first two years of follow-up did not appreciably change the results above.

3.4 Discussion

In this large population-based prospective study, we did not find any detrimental effect of coffee consumption on the risk of HF in either men or women. Actually, in women low-to-moderate amount of coffee drinking was associated with a reduced risk of HF.

To the best of our knowledge, only two studies have assessed the association between coffee consumption and the risk of HF, and both studies included Swedish men.(Ahmed et al., 2009; Wilhelmsen et al., 2001) The results of the present study support the findings of prior work that coffee consumption is not significantly associated with the risk of HF in men. (Ahmed et al., 2009) Moreover, for the first time, the present study also included women and observed a decreased risk of HF in women with low-to-moderate coffee consumption (1-6 cups daily). According to international statistics, the Finnish population has the highest per capita coffee consumption in the world, at 11.4 kg/year.(World Resources Institute) Research into the potential health effects of coffee in this population is therefore of particular interest.

Although the mechanism behind the association between coffee consumption and the risk of HF among women is incompletely understood, several putative mechanisms have been proposed. Because HF and CHD share risk factors such as: hypertension, diabetes, obesity, and smoking, CHD is regarded as a more common etiology in HF than ever before.(Fox KF, 1998; Wilhelmsen et al., 2001) In our study population, it has been previously shown that coffee drinking was associated with decreased CHD mortality(Kleemola et al., 2000) and the incidence of type 2 diabetes,(Tuomilehto et al.,

2004) whereas the lowest incidence of hypertension was found in people who did not drink coffee but no gradient in hypertension incidence with increasing coffee drinking was seen.(Hu et al., 2007b) Also, Wu et al.(Wu et al., 2009) reported that their meta-analysis of 21 prospective cohort studies on the association between coffee consumption and the risk of CHD did not support the hypothesis that coffee consumption increases the long-term risk of CHD, and habitual moderate coffee drinking was associated with a lower risk of CHD in women.(Wu et al., 2009) Their findings on the relationship between coffee consumption and the risk of CHD are similar with our findings about the association between coffee consumption and the risk of HF. Therefore, the effect of coffee consumption on HF may be partly mediated by its effect on other risk factors for CHD. In our study, the adjustment for the history of myocardial infarction and other CHD risk factors attenuated the association between coffee consumption and HF risk, and the association still remained significant among women but not among men.

The reason for the gender difference we have observed in the association between coffee consumption and HF risks is unclear. This finding is however in keeping with the finding of the observation regarding CHD mortality based on these same data: inverse association in women while no association in men.(Kleemola et al., 2000) Many epidemiologic studies have demonstrated that it is more likely for smokers than non-smokers to have more unhealthy lifestyle habits (e.g., physical inactivity, alcohol abuse).(Aasland and Nylenna, 1997) In the present study, coffee consumption was directly associated with smoking, and the prevalence of smoking was much higher among men than women. Although smoking was adjusted in our study, not all smoking-related unhealthy lifestyle habits were controlled.

Therefore, one explanation involved is that the difference in the prevalence of smoking between men and women and smoking related unhealthy lifestyle habits may be partially responsible for the observed gender difference in the association between coffee consumption and HF risk.(Wu et al., 2009)

There are mainly three categories of functional compounds in coffee: caffeine, antioxidants, and trace elements. Caffeine, a major component of coffee, prevents adenosine's negative inotropic effect as an adenosine-receptor antagonist(Van Soeren and Graham, 1998) and increases the sensitivity of the myofilaments to calcium.(Hess and Wier, 1984) Also, caffeine decreases insulin sensitivity(Keijzers et al., 2002) and increases serum homocysteine levels(Verhoef et al., 2002) and blood pressure.(Noordzij et al., 2005) In addition, caffeine stimulates free fatty acid release from peripheral tissues.(Ryu et al., 2001) On the other hand, antioxidants, obtained from coffee, like chlorogenic acid, phenolic compounds, flavonoids, melanoidins, and various lipid-soluble compounds such as furans, pyrroles, and maltol have beneficial antioxidant effects and might improve insulin sensitivity.(Arnlov et al., 2004) Trace elements in coffee such as potassium, niacin, and magnesium have beneficial effects on glucose and insulin metabolism,(Natella et al., 2002) improve insulin sensitivity,(Arnlov et al., 2004) decrease low-grade inflammation,(Lopez-Garcia et al., 2006) and lower diabetes risk.(van Dam and Hu, 2005) In our prior work, we observed an inverse and graded association between coffee consumption and type 2 diabetes,(Tuomilehto et al., 2004) which is recognized as one of the risk factors of HF.

There are several strengths and limitations in our study. First, a large number of both men and women from a homogeneous population participated in the study. Second, the mean follow-up was sufficiently long to ascertain a large number of HF endpoint events. We also carried out additional analyses excluding the subjects who died during the first two years of follow-up to avoid a potential bias due to a possible change in coffee consumption with severe disease. A limitation of our study was that we used self-report data on coffee intake only at baseline. However, the misclassification of exposure during the follow-up is most probably not systematically related to the outcome. Second, we did not assess the effect of caffeine on the risk of coffee consumption since we did not have available information about other main sources of caffeine, i.e. the consumption of cola beverage and chocolate. Third, even though our analyses were adjusted for physical activity, smoking, tea, and alcohol intake, residual confounding due to the measurement error in the assessment of confounding factors, unmeasured factors such as diet, cannot be excluded. In general, the associations between coffee consumption and HF risk were not influenced substantially or systematically. Finally, ascertainment of HF status was based on the National Hospital Discharge Registry, the National Social Insurance Institution's Register on special reimbursement for HF drugs, and Causes of Death Register. This diagnosis method has been used in other Scandinavian countries, such as Finland and Sweden.(Ingelsson et al., 2005a; Wang et al.) The accuracy of the HF cases in the Swedish hospital discharge is found to be over 80% based on the ESC definition.(Ingelsson et al., 2005a) Although accuracy of clinical HF diagnosis in our cohort is likely to be high, some diagnostic errors are inevitable. However, the misdiagnosis is most

likely to be independent of the exposure status and therefore tends to attenuate the underlying associations rather than cause spurious associations.

In conclusion, our study confirms that coffee consumption does not increase the risk of HF in Finnish men and women who have the highest consumption of coffee in the world. In women, we observed an inverse association between low-to-moderate coffee consumption and the risk of HF.

CHAPTER 4. LIFESTYLE FACTORS IN RELATION TO HEART FAILURE AMONG FINNISH MEN AND WOMEN[4]

4.1. Introduction

Heart failure (HF) poses a great threat to people around the world with its high prevalence, poor clinical outcomes, and large health-care costs.(Krum and Abraham, 2009; Sharp and Doughty, 1998) Except for the medical treatments for the cardiovascular risk factors of HF, modifiable lifestyle factors can also affect the development of HF. Compared with medical intervention, the prevention of HF through lifestyle approaches is free of side effect. Modifiable lifestyle factors like smoking,(Djousse et al., 2009; Eriksson et al., 1989a; He et al., 2001; Hoffman et al., 1994; Wilhelmsen et al., 2001) physical activity,(Djousse et al., 2009; Hu et al., 2010b; Kenchaiah et al., 2009; Wang et al., 2010b) adiposity,(Djousse et al., 2009; Hu et al., 2010b; Kenchaiah et al., 2002; Kenchaiah et al., 2009; Levitan et al., 2009a) alcohol consumption,(Abramson et al., 2001; Bryson et al., 2006; Djousse et al., 2009; Djousse and Gaziano, 2007a; Walsh et al., 2002) and dietary intake,(Djousse et al., 2009; Wang et al., 2011b) have been shown to influence the risk of HF in several studies. In the only epidemiological investigation related to the joint effect of these modifiable lifestyle factors on HF risk,(Djousse et al., 2009) engaging in healthy lifestyle factors was associated with the remaining lifetime risk of HF in men. However, it is unclear if this observed finding is generalizable to other populations and to both sexes. In order to gain a more comprehensive understanding of the effect of engaging in lifestyle factors on HF risk, we aim to examine the

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single and combined effects of smoking, body mass index (BMI), physical activity, and vegetable intake on HF risk in a large prospective cohort of Finnish men and women.

4.2 Methods

Subjects

Five independent cross-sectional population-based health examination surveys (FINRISK) were carried out in six geographic areas of Finland in 1982, 1987, 1992, 1997 and 2002.(Vartiainen et al.) The original random sample was stratified by area, gender and 10-year age group according to the World Health Organization (WHO) MONICA (MONItoring trends and determinants of CArdiovascular disease) protocol.(Pajak et al., 1988) The participation rate varied by year from 65% to 88%.(Vartiainen et al.) The subjects included in the five surveys were 25 to 64 years of age, and the 1997 and 2002 surveys also included subjects aged 65 to 74 years. Subjects who participated in more than one survey were included only in the first survey cohort. The total sample size of the five surveys was 38,737. The final sample comprised 18,346 men and 19,729 women after excluding the participants with a history of HF (n=457) at baseline, and the participants with incomplete data on any variables required for this analysis (n=205). The participants gave an informed consent (verbal from 1982 to 1992 and written in 1997 and 2002). These surveys were conducted according to the ethical rules of the National Public Health Institute, and the investigations were performed in accordance with the Declaration of Helsinki.

Baseline measurements

A self-administered questionnaire was mailed to the participants to be completed at home and returned to the survey site. The questionnaire included questions on medical history,

socioeconomic factors, physical activity, smoking habits, dietary intake, and alcohol consumption. Education level, measured as the total number of school years, was divided into birth cohort-specific tertiles. Data on the history of myocardial infarction or diabetes mellitus at baseline were obtained from the questionnaire and collected by hospital discharge diagnosis or drug register. Data on the use of antihypertensive agents at baseline were obtained from the questionnaire and drug register. Data on the history of valvular heart disease at baseline were collected by hospital discharge register.(Hu et al., 2010b; Hu et al., 2003; Wang et al., 2010b; Wang et al., 2011b)

A detailed description of the questions on occupational and leisure-time physical activity has been presented elsewhere.(Hu et al., 2003; Wang et al., 2010b) Since we found that moderate and high occupational or leisure time physical activity independently and significantly reduces risk of HF,(Hu et al., 2010b; Wang et al., 2010b) the groups were merged into three categories: “low” when subjects reported light levels of both occupational and leisure time physical activity; “moderate” when subjects reported moderate or high level of either occupational or leisure time physical activity; and “high” when subjects reported moderate or high level of both occupational and leisure time physical activity. Participants were classified as never, ex- and current-smokers based on their responses to the questionnaire. Alcohol consumption was categorized into four groups: none, 0.1-35, 35.1-70, and >70 g per week. The frequency of consumption of vegetables and fruits over the last week (<1 time/week, 1-2 times/week, 3-6 times/week, ≥7 times/week) were also inquired.(Hu et al., 2007d)

At the survey site, specially trained research nurses measured participants' height and weight by using the standardized WHO MONICA protocol.(Pajak et al., 1988) Height and weight were measured without shoes and with light clothing. The measurements of height were rounded to the nearest centimeter and weight to nearest 100 grams.(Pajak et al., 1988) BMI was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured from the right arm after five minutes of sitting using a mercury sphygmomanometer in each survey. After blood pressure measurement, a venous blood specimen was taken. Total cholesterol was determined by an enzymatic method (CHOD-PAP, Boehringer MANNHEIM, Mannheim, Germany). All samples were analyzed in the same central laboratory at the National Public Health Institute.

Prospective follow-up

Follow-up information was from the Finnish Hospital Discharge Register and the National Social Insurance Institution's Register on special reimbursement for HF drugs for non-fatal outcomes and the Finnish Causes of Death Register for fatal outcomes by record linkage using the personal identification numbers assigned to every citizen of Finland. The International Classification of Diseases (ICD) codes 427.00 and 427.10 (ICD-8), 428, 4029B (hypertensive heart disease with HF) and 4148A-X (ischemic HF with chronic coronary heart disease [CHD]) (ICD-9), and I 50, I11.0 (hypertensive heart disease with HF), I13.0 and I13.2 (hypertensive heart and renal disease with HF) (ICD-10) were used to identify HF cases in the above-mentioned national databases. A HF diagnosis was made by the treating physicians, based on a clinical assessment and examinations as considered relevant by the clinician in charge of treatment. Follow-up of each cohort member continued until the date of the

diagnosis of HF from the Hospital Discharge Register, Causes of death register or from the National Social Insurance Institution's Drug reimbursement Register or death resulting from causes other than HF, or December 31, 2007. This method to ascertain HF cases in prospective epidemiological studies has been used in Scandinavian countries, such as Sweden and Finland.(Ingelsson et al., 2005a; Levitan et al., 2009a; Wang et al., 2010a) A study from Sweden found the positive predictive value of HF diagnosis to be 82% (false positive rate 18%).(Ingelsson et al., 2005a) Another study from Finland also found the specificity of the HF diagnoses to be acceptable for the epidemiological study.(Wang et al., 2010a)

Statistical analyses

Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% confidence intervals (CIs) for categories of each of the 6 modifiable lifestyle factor (smoking [never, ever, and current], BMI [normal weight:<25 kg/m^2, overweight: 25-29.9 kg/m^2, and obese: ≥30 kg/m^2], physical activity [low, moderate, and high], vegetable consumption [<1, 1-2, 3-6, and ≥7 times per week], fruit consumption [<1, 1-2, 3-6, and ≥7 times per week], and alcohol consumption [none, 0.1-35, 35.1-70, and >70 g per week]).

Next, each lifestyle factor was dichotomized as unhealthy vs healthy: smoking (current vs never or ever), BMI (≥25 vs <25 kg/m^2), physical activity (low vs moderate or high), and vegetable consumption (≤2 vs ≥3 times per week). Fruit consumption and alcohol consumption were dropped out of the analyses because no significant associations with HF risk were found. Given that healthy lifestyle factors were defined as never or ever smoking, BMI <25 kg/m^2, moderate or high levels of physical activity, and consumption of vegetable ≥3 times per week, each person could have a minimum of 0 and maximum of 4 healthy lifestyle

factors. Differences in the general characteristics of study subjects who had 0, 1, 2, 3 or 4 healthy lifestyle factors were tested using General Linear Models after adjustment for age and study year. The number of healthy lifestyle factors was included in the Cox proportional hazards regression models as dummy and categorical variables, and the significance of the trend over different categories was tested in the same models by giving an ordinal numeric value for each dummy variable. The proportional hazards assumption in the Cox model was assessed with graphical methods, and with models including time-by-covariate interactions.(Cox, 1972) In general, all proportionality assumptions were appropriate.

All the above analyses were first carried out adjusting for age and study year, and further for education, systolic blood pressure, total cholesterol, and histories of myocardial infarction, valvular heart disease, diabetes, and using antihypertensive drugs**.** To avoid a potential bias due to severe disease at baseline, additional analyses were carried out excluding the subjects who died during the first two years of follow-up (n=290). Statistical significance was considered to be $P<0.05$. All the above statistical analyses were performed with PASW for Windows, version 18.0 (SPSS Inc, Chicago, III).

To estimate the proportion of new HF cases occurring in this population that hypothetically could have been prevented if all subjects had been in the healthy lifestyle group, while the distribution of other modifiable and non-modifiable risk factors is unchanged, the partial population attributable risk percent (PAR%) (Spiegelman et al., 2007) and 95% CI were calculated by using SAS for Windows, version 9.12 (SAS Institute, Cary, NC).

4.3 Results

During a median follow-up of 14.1 years (interquartile range 5.9-20.9 years), 638 men and 445 women developed HF. General characteristics of the study population at baseline are presented by the number of healthy lifestyle factors in Table 10.

Except for fruit consumption and alcohol consumption, the other individual components of the lifestyle factors were independently and significantly associated with the risk of HF when they were simultaneously entered into the multivariable model (Table 11). The most important risk factor for HF was smoking status; the HR of HF was 1.86 (95% CI 1.51-2.30) for men and 2.09 (95% CI 1.59-2.74) for women who were current smoker, as compared with subjects who never smoked. Overweight or obesity was also associated with a significantly increased HF risk, while engagement in moderate-to-high levels of physical activity, the consumption of vegetable more than three times per week were associated with a significantly decreased HF risk.

In both age and study year-adjusted analysis and the multivariable-adjusted (age, study year, education, systolic blood pressure, total cholesterol, and histories of myocardial infarction, valvular heart disease, diabetes, and using antihypertensive drugs) analysis, a dose-response relationship between the combinations of the 4 healthy lifestyle factors (physical activity, smoking, BMI, and vegetable consumption) and the hazard ratios of HF was observed (Table 12). The partial PAR% associated with engaging in any 3 or 4 of the healthy lifestyle indicators were 45.6% (95% CI 36.5% - 53.8%) and 53.6% (95% CI 31.3% - 70.2%), respectively, suggesting that 45.6% or 54.1% of new HF cases occurring in this population could have been prevented if all subjects had any 3 or 4 of the healthy lifestyle

Table 10. General characteristics of study at baseline*

	No. of healthy lifestyle factors†					
	0	1	2	3	4	P for trend
Men						
No. of subjects	1,473	5,267	6,633	3,969	1,004	
Age at baseline (yrs)	47.5 (11.7)	48.7 (12.5)	47.2 (12.5)	44.3 (11.8)	41.4 (10.6)	<0.001
Body mass index (kg/m2)	29.1 (3.4)	27.8 (4.0)	26.9 (3.8)	25.3 (3.4)	23.2 (1.4)	<0.001
Current smoker (%)	100	53.8	28.3	11.5	0.0	<0.001
Moderate or high physical activity (%)	0.0	16.7	41.8	70.2	100	<0.001
Vegetable consumption ≥3 time/week (%)	0.0	18.5	55.8	82.8	100	<0.001
Alcohol consumption (g/week)	107 (154)	89 (146)	77 (113)	67 (92)	56 (70)	<0.001
Diastolic blood pressure (mm Hg)	87 (12)	86 (12)	85 (12)	83 (11)	80 (11)	<0.001
Systolic blood pressure (mm Hg)	145 (19)	143 (19)	141 (19)	138 (18)	135 (17)	<0.001
Serum cholesterol (mmol/l)	6.13 (1.17)	6.00 (1.18)	5.81 (1.15)	5.66 (1.13)	5.46 (0.99)	<0.001

Table 10 continued

Education (yrs)	9.3 (3.3)	9.7 (3.8)	10.7 (4.0)	11.5 (4.0)	11.8 (3.7)	<0.001
History of myocardial infarction (%)	5.6	4.8	3.8	2.9	3.1	<0.001
History of valvular heart disease (%)	0.1	0.2	0.2	0.2	0.2	0.767
History of diabetes (%)	3.1	3.2	2.8	2.5	1.9	0.124
History of using anti-hypertensive drugs (%)	12.8	13.7	12.8	8.5	4.1	<0.001
Women						
No. of subjects	500	3,573	7,189	6,227	2,240	
Age at baseline (yrs)	44.9 (12.0)	48.8 (12.6)	47.8 (12.6)	44.0 (11.4)	41.0 (9.8)	<0.001
Body mass index (kg/m2)	29.9 (4.3)	28.9 (5.2)	27.1 (4.9)	24.5 (4.0)	22.4 (1.7)	<0.001
Current smoker (%)	100.0	41.5	21.5	8.9	0	<0.001
Moderate or high physical activity (%)	0.0	5.3	19.9	52.7	100.0	<0.001
Vegetable consumption ≥3 time/week (%)	0.0	19.5	67.8	89.0	100.0	<0.001
Alcohol consumption (g)	40 (65)	25 (51)	26 (50)	25 (41)	23 (36)	<0.001

Table 10 continued

Diastolic blood pressure (mm Hg)	83 (12)	82 (11)	81 (11)	79 (11)	71 (10)	<0.001
Systolic blood pressure (mm Hg)	137 (20)	140 (22)	137 (21)	132 (20)	128 (17)	<0.001
Serum cholesterol (mmol/l)	5.94 (1.25)	5.99 (1.26)	5.81 (1.22)	5.56 (1.13)	5.35 (1.03)	<0.001
Education (yrs)	9.8 (3.1)	9.5 (3.6)	10.7 (3.9)	12.0 (3.9)	12.7 (3.6)	<0.001
History of myocardial infarction (%)	1.9	2.0	1.0	0.6	0.6	<0.001
History of valvular heart disease (%)	0.2	0.1	0.1	0.1	0.1	0.872
History of diabetes (%)	2.5	2.7	2.6	1.6	1.1	<0.001
History of using anti-hypertensive drugs (%)	12.0	15.6	14.1	7.6	3.2	<0.001

*Values are given as mean (SD) when appropriate.

†Four modifiable lifestyle factors included smoking, body mass index, physical activity, and vegetable consumption.

Table 11. Hazard ratios of heart failure according to lifestyle factors

	Men			P for	Women			P for
Lifestyle factors	No. of cases	Person-yrs	Multivariable adjustment HR (95% CI)* †	trend	No. of cases	Person-yrs	Multivariable adjustment HR (95% CI)* †	trend
Physical activity				0.006				0.009
Light	128	27,863	1.00		129	44,435	1.00	
Moderate	334	118,082	0.79 (0.64-0.97)		229	138,989	0.87 (0.70-1.08)	
High	176	115,186	0.67 (0.53-0.86)		87	109,288	0.64 (0.48-0.86)	
Smoking status				<0.001				<0.001
Never	153	98,111	1.00		347	201,982	1.00	
Ever	213	67,484	1.06 (0.86-1.31)		25	32,189	1.02 (0.68-1.55)	
Current	272	95,537	1.86 (1.51-2.30)		73	58,542	2.09 (1.59-2.74)	
Alcohol consumption (g/week)								
0	272	94,275	1.00	0.225	346	170,956	1.00	0.899

Table 11 continued

0.1-35	75	34,306	0.91 (0.70-1.18)		54	54,170	0.90 (0.67-1.21)	
35.1-70	92	40,378	1.00 (0.79-1.27)		30	38,268	1.01 (0.68-1.50)	
>70	199	92,173	1.17 (0.96-1.42)		15	29,318	0.92 (0.53-1.57)	
Body mass index (kg/m2)				<0.001				<0.001
<25	142	95,701	1.00		97	145,836	1.00	
25-29.9	293	122,376	1.15 (0.93-1.41)		155	95,847	1.21 (0.93-1.57)	
≥30	203	43,055	1.75 (1.40-2.20)		193	51,030	2.06 (1.59-2.67)	
Fruit consumption (time/week)				0.471				0.799
<1	109	36,062	1.00		48	18,735	1.00	
1-2	261	99,472	1.14 (0.91-1.44)		133	71,441	0.89 (0.63-1.24)	
3-6	153	74,523	1.00 (0.77-1.30)		129	89,447	0.92 (0.65-1.29)	
≥7	115	51,074	1.11 (0.83-1.47)		135	113,090	0.85 (0.60-1.20)	
Vegetable consumption (time/week)				0.047				0.153

Table 11 continued

<1	162	41,126	1.00	74	20,714	1.00
1-2	258	95,067	0.88 (0.72-1.08)	162	80,296	0.89 (0.67-1.18)
3-6	148	81,316	0.74 (0.58-0.94)	123	109,376	0.73 (0.54-0.99)
≥7	70	43,623	0.70 (0.51-0.96)	86	82,328	0.93 (0.60-1.31)

*HR = hazard ratio; CI = confidence interval.

†Adjusted for age, study year, smoking, vegetable consumption, fruit consumption, education, alcohol consumption, history of myocardial infarction, history of valvular heart disease, history of diabetes, history of using anti-hypertensive drugs, BMI, systolic blood pressure, and total cholesterol, other than the variable in the analytic model.

Table 12. Hazard ratios of heart failure according to number of healthy lifestyle factors restricted to adiposity, smoking, physical activity, and vegetable consumption

	men				women			
No. of healthy lifestyle factors	No. of cases	Person-yrs	Age and study years adjusted HR (95% CI) *	Multivariable adjustment HR (95% CI) †	No. of cases	Person-yrs	Age and study years adjusted HR (95% CI)	Multivariable adjustment HR (95% CI) †
0	97	19,441	1.00	1.00	20	7,009	1.00	1.00
1	271	72,805	0.64 (0.50-0.80)	0.68 (0.54-0.86)	168	53,030	0.59 (0.37-0.94)	0.53 (0.33-0.85)
2	191	93,954	0.39 (0.31-0.50)	0.44 (0.35-0.57)	185	104,487	0.43(0.27-0.69)	0.42 (0.27-0.67)
3	67	59,020	0.28 (0.20-0.38)	0.33 (0.24-0.45)	61	93,757	0.24 (0.14-0.39)	0.24 (0.14-0.40)
4	12	15,912	0.25 (0.14-0.46)	0.30 (0.16-0.54)	11	34,431	0.18 (0.08-0.37)	0.19 (0.09-0.40)
P for trend			<0.001	<0.001			<0.001	<0.001

*HR = hazard ratio; CI = confidence interval.

†Adjusting for age, study year, education, history of myocardial infarction, history of valvular heart disease, history of diabetes, history of using anti-hypertensive drugs, systolic blood pressure, and total cholesterol.

indicators. However, since PAR% assumes the lifestyle factors are causal, it should be interpreted with caution.

Exclusion of the participants who died during the first two years of follow-up did not appreciably change the results above.

4.4 Discussion

In the present study, we observed that maintaining a BMI ≤25, consuming vegetable ≥3 times a week, abstaining from smoking and engaging in moderate or high level of physical activity were individually and jointly associated with a decreased risk of HF among both men and women. Furthermore, the dose-response relationship between the number of healthy lifestyle factors one engaged in and HF risk suggested that the closer one was engaging in a healthy lifestyle, the further the risk of HF was reduced.

Smoking, which was identified as the most powerful predictor of incident HF in the current cohort, was first shown to be the major independent risk factor of HF in a study (Eriksson et al., 1989a) conducted on 973 men born in 1913 in Gothenburg, Sweden. The authors found that smoking at age 50 was associated with a 60% higher risk of Congestive HF (RR, 1.6; 95%, 1.2-3.2), and this relationship was independent of hypertension and other important risk factors of Congestive HF. The finding has been confirmed by several other studies conducted on different population.(He et al., 2001; Hoffman et al., 1994; Wilhelmsen et al., 2001) Based on the evidence revealing the positive association between smoking and HF, the European Society of Cardiology, American College of Cardiology, and American Heart Association identified smoking as one of the risk factors as well as one of the targets of

prevention and management of HF in their guidelines.(Dickstein et al., 2008; Hunt et al., 2005; Schocken et al., 2008b)

The relation of physical activity(He et al., 2001; Hu et al., 2010b; Kenchaiah et al., 2009; Wang et al., 2010b) and obesity(Bahrami et al., 2008; Chen et al., 1999; He et al., 2001; Hu et al.; Ingelsson et al., 2005b; Ingelsson et al., 2005c; Kenchaiah et al., 2002; Kenchaiah et al., 2009; Levitan et al., 2009a; Loehr et al., 2009) to HF has been studied extensively. The results from these prospective studies consistently indicate that regular physical activity reduces the risk of HF, while both general obesity and abdominal obesity increase the risk of HF. Furthermore, research (Hu et al., 2010b; Kenchaiah et al., 2009) related to the joint effect of obesity and physical activity on HF risk indicates that lean and active individuals had the lowest HF risk. Therefore, preventing of HF by maintaining optimal weight and involving in regular physical activity may be promising in reducing the public health burden of HF worldwide.

Although dietary pattern and food choices have been associated with risk factors for HF such as hypertension, CHD and type 2 diabetes, the role of diet on HF has not been studied adequately to date. Djousséea al (Djousse et al., 2009; Djousse and Gaziano, 2007b) have done extensive work to evaluate the associations between dietary factors on the risk of HF by using the data from the Physicians' Health Study: their studies showed that fruit and vegetable consumption (Djousse et al., 2009) and whole-grain breakfast cereals consumption (Dhingra et al., 2010) were associated with a reduced risk of HF. The Swedish Mammography Cohort showed that diets consistent with the DASH diet, a diet features high intake of fruits, vegetables, low-fat dairy products, and whole grains, were associated with a decreased risk of

HF.(Levitan et al., 2009b) In the current study, fruit consumption was not associated with the risk of HF which is different from the findings from the study conducted by Djousséa al.(Djousse et al., 2009) The inconsistency might be partly explained by the different questionnaires used to assess fruit consumption, and the differences in the dietary habits between the Finish population and Americans. All these studies together with the current study suggest that the prevention of HF through dietary approaches should be stressed.

The studies that have addressed alcohol consumption and the risk of HF have yielded inconsistent results.(Abramson et al., 2001; Bryson et al., 2006; Djousse et al., 2009; Djousse and Gaziano, 2007a; Walsh et al., 2002) Like us, Bryson et al(Bryson et al., 2006) did not find a significant association between alcohol consumption and the risk of HF. In contrast, several studies(Abramson et al., 2001; Bryson et al., 2006; Djousse et al., 2009; Walsh et al., 2002) showed that moderate alcohol consumption was associated with a reduced risk of HF, whereas alcohol abuse was associated with a higher risk of HF.(Wilhelmsen et al., 2001) The discrepancy among these findings may be partly explained by the different assessment of alcohol consumption, and the age and race difference between the study samples of these studies. In order to establish the association between alcohol consumption and HF and make appropriate recommendations to the general public especially those at high risk for HF, further studies are needed.

To the best of our knowledge, the only study(Djousse et al., 2009) addressing the association between the joint effect of modifiable lifestyle factors on HF risk was conducted among male physicians who are more aware of the consequences of unhealthy lifestyle than the general public. The results of the present study support their finding that engaging in

healthy lifestyle factors is associated with a lower HF risk in men. Moreover, for the first time, the present study demonstrated a similar association in women. Although each of these 4 modifiable lifestyle factors has been shown to be independently associated with the risk of HF in various studies, the general public does not have enough awareness of these associations, and the prevalence of unhealthy lifestyle continues to be high. Large social and community-based lifestyle intervention may help to prevent and manage HF.

There are several strengths and limitations in our study. First, a major strength of the study is the large number of both men and women from a homogeneous population who participated in the study. Second, the follow-up time was sufficiently long to ascertain a large number of HF endpoint events. Finally, we also carried out additional analyses excluding the subjects who died during the first two years of follow-up to avoid a potential bias due to a severe disease at baseline. A limitation of our study is that information on self-reported physical activity, smoking habits, vegetable and alcohol consumptions was recorded only once at baseline. We have no data on possible changes in the lifestyle factors during the follow-up. However, the misclassification of the levels of these lifestyle factors during the follow-up is most probably not systematically related to the outcome, but may weaken the observed association. Ascertainment of HF status was based on the National Hospital Discharge Registry, the National Social Insurance Institution's Register on special reimbursement for HF drugs, and Causes of Death Register. These data are primarily collected for administrative purposes and not for a scientific study. There are guidelines for assigning diagnoses in these register and established quality control procedures, but the diagnoses may vary over time and between the hospitals. This method for ascertaining the HF outcome has, however, been

successfully used in prior studies in Scandinavian countries, such as Finland and Swede.(Hu et al., 2010b; Ingelsson et al., 2005a; Levitan et al., 2009a; Wang et al., 2010a; Wang et al., 2010b; Wang et al., 2011b) Also, we cannot completely either exclude the effects of residual confounding due to measurement error in the assessment of confounding factors, or some unmeasured dietary factors. An additional limitation is the use of the healthy lifestyle point system. Each healthy lifestyle factor was weighted the same which implies that each is equally important, though the results indicated that smoking was the strongest risk factor for HF. This may lead to heterogeneous people being in the same category.

In conclusion, there was a graded inverse association between the number of healthy lifestyle factors and the risk of HF in Finnish men and women. Therefore, in order to reduce the incidence of HF, more efforts should be put into promoting healthy lifestyles and their associated health benefits.

CHAPTER 5. HEALTHY LIFESTYLE STATUS, ANTIHYPERTENSIVE TREATMENT AND THE RISK OF HEART FALIURE AMONG FINNISH MEN AND WOMEN[5]

5.1 Introduction

Heart failure (HF), which lead to 3,434,000 clinical visits in 2007 in the U.S,(Schappert and Rechtsteiner, 2011) has become a major health problem. According to the American Heart Association (AHA),(Roger et al., 2011) 1 in 9 death certificates (277,193 deaths) in the U.S. included heart failure as a contributing cause of death in 2007.

Hypertension is one of the major risk factors of HF: 75% of HF cases have antecedent hypertension.(Lloyd-Jones et al., 2002) However, there is little information on the risk of HF in treated hypertensive people, controlled or uncontrolled for their blood pressure compared with normotensive individuals followed over a long period. Also, data from our recent publication(Wang et al., 2011a) demonstrated a graded inverse association between number of healthy lifestyle traits (maintaining a body mass index [BMI] ≤25, consuming vegetables ≥3 times a week, abstaining from smoking and engaging in moderate or high level of physical activity) and the risk of HF in the Finnish general population.

Ideal cardiovascular health is now defined by the presence of the traditional health factors (untreated total cholesterol <200 mg/dL, untreated blood pressure <120/<80 mm Hg, and fasting blood glucose <100 mg/dL) as well as ideal health behavioral factors (nonsmoking, BMI <25 kg/m^2, physical activity at goal levels, and pursuit of a diet consistent with current guideline recommendations) according to a recent special report of the

[5] This chapter originally appeared as Yujie Wang, Jaakko Tuomilehto, Pekka Jousilahti, Riitta Antikainen, Markku Mähönen, Peter T. Katzmarzyk, and Gang Hu. Healthy lifestyle status, antihypertensive treatment and the risk of heart failure among Finnish men and women. Accepted by Journal of Hypertension on June 10, 2013. Reprinted by permission of Wolters Kluwer Health.

AHA.(Lloyd-Jones et al., 2010) One study has demonstrated that a healthy lifestyle significantly decreases stroke risk in different strata of hypertension status and antihypertensive drug treatments.(Zhang et al., 2012) However, based on the available evidence, it is unclear that which is more effective in preventing HF in hypertensive people: lifestyle intervention or antihypertensive drug treatment. Therefore, this study aimed to investigate 1) whether there are differences in HF risk among hypertensive men and women using antihypertensive drug treatment at baseline versus those engaging in a healthy lifestyle at baseline, and 2) whether there are differences in HF risk among hypertensive men and women by awareness, treatment and blood pressure control status at baseline.

5.2 Methods

Participants

Five independent cross-sectional population-based health examination surveys (the National FINRISK Study) were carried out in five geographic areas of Finland in 1982, 1987, 1992, 1997 and 2002.(Vartiainen et al.) The original random sample was stratified by area, gender and 10-year age group according to the World Health Organization (WHO) MONICA (MONItoring trends and determinants of CArdiovascular disease) protocol.(Pajak et al., 1988) The participation rate varied by year from 65% to 88%.(Vartiainen et al.) The subjects included in the five surveys were 25 to 64 years of age, and the 1997 and 2002 surveys also included subjects aged 65 to 74 years. Subjects who participated in more than one survey were included only in the first survey cohort. The total sample size of the five surveys was 38,737. The final sample comprised 18,346 men and 19,729 women after excluding the participants with a history of HF (n=457) at baseline, and the participants with incomplete data on any

variables required for this analysis (*n*=205). The participants provided informed consent (verbal from 1982 to 1992 and written in 1997 and 2002). These surveys were conducted according to the ethical rules of the National Public Health Institute, and the investigations were performed in accordance with the Declaration of Helsinki.

Baseline measurements

A self-administered questionnaire was mailed to the participants to be completed at home and returned to the survey site. The questionnaire included questions on medical history, socioeconomic factors, physical activity, smoking habits, dietary intake, and alcohol consumption. Education level, measured as the total number of school years, was divided into birth cohort-specific tertiles. Data on the history of myocardial infarction or diabetes mellitus at baseline were obtained from the questionnaire and collected by hospital discharge diagnosis or drug register. Data on the use of antihypertensive agents at baseline were obtained from the questionnaire and drug register. Data on the history of valvular heart disease at baseline were collected by hospital discharge register.(Hu et al., 2010b; Hu et al., 2003; Wang et al., 2010b, 2011a; Wang et al., 2011b) A detailed description of the questions on lifestyle factors including physical activity, smoking, and vegetable consumption has been presented elsewhere.(Hu et al., 2003; Wang et al., 2010b, 2011a) Alcohol consumption was categorized into four groups: none, 0.1-35, 35.1-70, and >70 g per week.

At the survey site, specially trained research nurses measured participants' height and weight by using the standardized WHO MONICA protocol.(Pajak et al., 1988) Height and weight were measured without shoes and with light clothing. The measurements of height were rounded to the nearest centimeter and weight to nearest 100 grams.(Pajak et al., 1988)

BMI was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured twice from the right arm after five minutes of sitting using a mercury sphygmomanometer, and the mean of these two blood pressures was used in the analyses. A person was considered to have hypertension when the average blood pressure was at least 140 mmHg systolic and/or 90 mmHg diastolic or if he/she reported having taken antihypertensive drugs during the preceding 7 days.(Hu et al., 2005a) Awareness of hypertension was defined as a participant having reported a previous diagnosis of hypertension or current use of antihypertensive drug treatment. People on antihypertensive drug treatment, whose measured blood pressure level was < 140/90 mmHg, were considered to be adequately treated (controlled). The study population was classified into five groups according to their blood pressure status at baseline: normotensive participants, unaware and untreated hypertensive patients, hypertensive people aware of their hypertensive status but untreated, patients treated with antihypertensive drugs and adequately treated, patients treated with antihypertensive drugs but not controlled. After blood pressure measurement, a venous blood specimen was taken. Total cholesterol was determined by an enzymatic method (CHOD-PAP, Boehringer MANNHEIM, Mannheim, Germany). All samples were analyzed in the same central laboratory at the National Public Health Institute.

In our previous publication, healthy lifestyle factors are defined as moderate or high level of physical activity, never smoking, BMI <25 kg/m^2, and vegetable consumption ≥3 times/week.(Wang et al., 2011a) Since we found a graded inverse association between the number of healthy lifestyle factors and the risk of HF,(Wang et al., 2011a) a healthy lifestyle was defined as having two or more healthy lifestyle factors.

Prospective follow-up

Follow-up information was from the Finnish Hospital Discharge Register and the National Social Insurance Institution's Register on special reimbursement for HF drugs for non-fatal outcomes and the Finnish Causes of Death Register for fatal outcomes by record linkage using the personal identification numbers assigned to every citizen of Finland. The International Classification of Diseases (ICD) codes 427.00 and 427.10 (ICD-8), 428, 4029B (hypertensive heart disease with HF) and 4148A-X (ischemic HF with chronic coronary heart disease) (ICD-9), and I 50, I11.0 (hypertensive heart disease with HF), I13.0 and I13.2 (hypertensive heart and renal disease with HF) (ICD-10) were used to identify HF cases in the above-mentioned national databases. A HF diagnosis was made by the treating physicians, based on a clinical assessment and examinations as considered relevant by the clinician in charge of treatment. Follow-up of each cohort member continued until the date of the diagnosis of HF from the Hospital Discharge Register, Causes of death register or from the National Social Insurance Institution's Drug reimbursement Register or death resulting from causes other than HF, or December 31, 2007. The overall positive predictive value of HF diagnosis in this FINRISK study was 85.9% (negative predictive value 97.9%).(Mahonen et al., 2012)

Statistical analyses

Differences in the general characteristics of study subjects by blood pressure and lifestyle status were tested using General Linear Models after adjustment for age, sex and study year. Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% confidence intervals (CIs) for the five different blood pressure groups and the two different

lifestyle groups. Next, participants were placed into 10 groups according to their blood pressure and lifestyle status at baseline. Cox proportional hazards regression was used to estimate the association between the ten groups and HF risk. Different blood pressure and lifestyle categories were included in the Cox proportional hazards regression models as dummy and categorical variables, and the significance of the trend over different categories was tested in the same models by giving an ordinal numeric value for each dummy variable. The proportional hazards assumption in the Cox model was assessed with graphical methods, and with models including time-by-covariate interactions.(Cox, 1972) In general, all proportionality assumptions were appropriate.

All the above analyses were first carried out adjusting for age, sex, study year, and further for education and alcohol consumption, and further for total cholesterol, and histories of myocardial infarction, valvular heart disease, and diabetes. To avoid a potential bias due to severe disease at baseline, additional analyses were carried out excluding the subjects who died during the first two years of follow-up (n=290). In order to determine if the definition of a healthy lifestyle used would influence the results, we did a sensitivity analysis whereby having three or four healthy lifestyle factors constituted a healthy lifestyle. Men and women were combined in the analyses because there was no significant gender difference. Statistical significance was considered to be $P<0.05$. All the above statistical analyses were performed with PASW for Windows, version 19.0 (SPSS Inc, Chicago, III).

5.3 Results

During a median follow-up of 14.1 years (interquartile range 5.9-20.9 years), 638 men and 445 women developed HF. General characteristics of the study population at baseline are presented by blood pressure and lifestyle status in Table 13.

After adjustment for age, sex, study year, education and alcohol consumption (multivariable model 2)**,** the risk of HF was significantly higher in subjects in all hypertensive groups compared with normotensive group, while the risk of HF was significantly lower in the group with a healthy lifestyle compared with the group without a healthy lifestyle (Table 14). Compared with the HF risk in the normotensive group, the risk of HF increased 39% for the hypertensive, unaware, and untreated group, 51% for the hypertensive, aware, and untreated group, 60% for the hypertensive, treated, and uncontrolled group, 71% for the hypertensive, treated, and controlled one. The risk of HF increased 84% among the group without a healthy lifestyle compared with the group with a healthy lifestyle. Further adjustment for total cholesterol, and histories of myocardial infarction, valvular heart disease, and diabetes affected these results only slightly.

Table 15 presents the HR of HF for subjects by different combinations of blood pressure and lifestyle status. The multivariable-adjusted (model 2) HRs of HF in the ten subgroups (1] normotensive group with a healthy lifestyle – reference group; 2] hypertensive, unaware, untreated group with a healthy lifestyle; 3] hypertensive, aware, untreated group with a healthy lifestyle; 4] hypertensive, treated, controlled group with a healthy lifestyle; 5] hypertensive, treated, uncontrolled group with a healthy lifestyle; 6] normotensive group without a healthy lifestyle; 7] hypertensive, unaware, untreated group without a healthy lifestyle; 8] hypertensive, aware, untreated group without a healthy lifestyle; 9] hypertensive,

Table 13. General characteristics of study subjects at baseline*

	Healthy lifestyle factors ≥ 2					Healthy lifestyle factors < 2					P value
	Normotensive	Hypertensive unaware and untreated	Hypertensive aware but untreated	Hypertensive treated and controlled	Hypertensive treated and uncontrolled	Normotensive	Hypertensive unaware and untreated	Hypertensive Aware but untreated	Hypertensive treated and control	Hypertensive treated and uncontrolled	
No. of subjects	14,859	5,797	3,815	553	2,238	4,359	3,075	1,853	269	1,257	
Age at baseline (yrs)	41.1	49.1	48.9	54.0	56.3	42.9	51.2	50.3	55.4	57.7	<0.001
Body mass index (kg/m^2)	24.8	26.0	27.0	27.9	28.4	27.3	28.2	29.4	30.2	30.2	<0.001
Diastolic blood pressure (mmHg)	76	86	92	80	91	76	87	93	78	92	<0.001
Systolic blood pressure (mmHg)	124	149	155	126	156	126	150	156	126	156	<0.001
Serum cholesterol (mmol/l)	5.59	5.89	5.89	5.62	5.77	5.83	6.05	6.08	5.75	5.87	<0.001
Education (yrs)	11.4	10.8	10.9	10.9	10.7	10.0	9.8	9.9	9.8	9.9	<0.001
Alcohol consumption (g/week)	43.6	50.0	53.2	45.6	49.8	55.4	68.9	75.2	53.0	61.7	<0.001
Low physical activity (%)	5.5	4.9	4.7	8.0	8.7	16.1	18.0	15.8	29.0	24.5	<0.001

Table 13 continued

Vegetable consumption ≥ 3 times/wk (%)	74.7	73.1	76.3	83.2	80.7	19.2	15.5	16.6	16.9	11.2	<0.001
Ever or current smoker (%)	39.1	37.0	37.5	41.7	37.4	74.1	67.8	64.7	65.5	59.6	<0.001
History of diabetes (%)	1.8	1.2	2.1	7.6	7.0	2.3	1.7	2.1	10.4	8.1	<0.001
History of myocardial infarction (%)	2.2	1.0	1.2	5.3	4.6	3.0	2.3	2.7	15.7	6.6	<0.001
History of valvular heart disease (%)	0.1	0.1	0.2	0.6	0.3	0.2	0.1	0.0	0.6	0.2	0.028

*Values represent mean or percentage; adjusted for age, sex and study year. Healthy lifestyle factors are defined as moderate or high level of physical activity, never smoking, body mass index < 25 kg/m^2, and vegetable consumption ≥ 3 times/week. Normotensive was defined as systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg and without antihypertensive drug treatment.

Table 14. Hazard ratios of heart failure by lifestyle factors and hypertensive status*

	No. of subjects	Case	Person-yrs	Model 1 HR (95% CI) †	Model 2 HR (95% CI) ‡	Model 3 HR (95% CI) §
Lifestyle factors						
Healthy lifestyle factors ≥ 2	27,262	527	401,561	1.00	1.00	1.00
Healthy lifestyle factors < 2	10,813	556	152,284	1.88 (1.67-2.13)	1.84 (1.63-2.08)	1.79 (1.58-2.02)
P trend				<0.001	<0.001	<0.001
Hypertensive status						
Normotensive	19,218	248	26,449	1.00	1.00	1.00
Hypertensive, unaware, untreated	8,872	397	125,835	1.39 (1.19-1.64)	1.39 (1.18-1.63)	1.40 (1.19-1.65)
Hypertensive, aware, untreated	5,668	208	198,441	1.52 (1.26-1.83)	1.51 (1.25-1.82)	1.49 (1.24-1.80)
Hypertensive, treated, controlled	822	31	152,777	1.63 (1.12-2.37)	1.60 (1.10-2.33)	1.34 (0.92-1.95)
Hypertensive, treated, uncontrolled	3,495	199	50,343	1.72 (1.42-2.09)	1.71 (1.41-2.07)	1.53 (1.26-1.86)
P trend				<0.001	<0.001	<0.001

*Normotensive was defined as systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg and without antihypertensive drug treatment.

†Adjusted for age, study year and sex.

‡Adjusted for age, study year, sex, education, alcohol consumption and lifestyle factors/hypertensive status.

§Adjusted for age, study year, sex, education, alcohol consumption, lifestyle factors/hypertensive status, total cholesterol, history of myocardial infarction, history of valvular heart disease and history of diabetes.

CI = confidence interval; HR = hazard ratio.

Table 15. Hazard ratios of heart failure in normotensive individuals* and in different categories of hypertensive individuals by different levels of lifestyle factors

	No. of subjects	Case	Person-yrs	Model 1 HR (95% CI) †	Model 2 HR (95% CI) ‡	Model 3 HR (95% CI) §
Healthy lifestyle factors ≥ 2						
Normotensive	14,859	135	220,224	1.00	1.00	1.00
Hypertensive, unaware, untreated	5,797	186	91,520	1.52 (1.21-1.90)	1.50 (1.20-1.88)	1.51 (1.21-1.89)
Hypertensive, aware, untreated	3,815	93	55,258	1.56 (1.19-2.03)	1.54 (1.18-2.01)	1.51 (1.16-1.97)
Hypertensive, treated, controlled	553	19	6,300	2.28 (1.41-3.70)	2.24 (1.39-3.64)	1.96 (1.21-3.18)
Hypertensive, treated, uncontrolled	2,238	94	28,259	1.93 (1.48-2.53)	1.91 (1.46-2.50)	1.69 (1.29-2.22)
Healthy lifestyle factors < 2						
Normotensive	4,359	113	61,093	2.18 (1.69-2.80)	2.12 (1.65-2.72)	2.03 (1.58-2.61)
Hypertensive, unaware, untreated	3,075	211	46,263	2.76 (2.21-3.45)	2.68 (2.14-3.35)	2.62 (2.09-3.28)
Hypertensive, aware, untreated	1,853	115	26,458	3.15 (2.45-4.05)	3.05 (2.37-3.93)	2.93 (2.27-3.77)
Hypertensive, treated, controlled	269	12	3,005	2.37 (1.31-4.29)	2.27 (1.25-4.11)	1.76 (0.97-3.19)
Hypertensive, treated, uncontrolled	1,257	105	15,465	3.32 (2.55-4.31)	3.21 (2.47-4.18)	2.80 (2.14-3.65)
P trend				<0.001	<0.001	<0.001

*Normotensive was defined as systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg and without antihypertensive drug treatment.
†Adjusted for age, study year and sex.
‡Adjusted for age, study year, sex, education, and alcohol consumption.
§Adjusted for age, study year, sex, education, alcohol consumption, total cholesterol, history of myocardial infarction, history of valvular heart disease and history of diabetes.
CI = confidence interval; HR = hazard ratio.

Table 16. Hazard ratios of heart failure by different lifestyle factors and hypertensive* subgroups

	No. of subjects	Case	Person-yrs	Model 1 HR (95% CI) †	Model 2 HR (95% CI) ‡	Model 3 HR (95% CI) §
Healthy lifestyle VS Medication						
Hypertensive, untreated, healthy lifestyle factors ≥ 2	9,612	279	146,777	1.00	1.00	1.00
Hypertensive, treated, healthy lifestyle factors < 2†	1,526	117	18,469	2.17 (1.73-2.70)	2.10 (1.68-2.63)	1.75 (1.39-2.21)
Healthy lifestyle + medication VS Non-healthy lifestyle + No medication						
Hypertensive, treated, healthy lifestyle factors ≥ 2	2,791	113	34,559	1.00	1.00	1.00
Hypertensive, untreated, healthy lifestyle factors < 2†	4,928	326	72,721	1.46 (1.17-1.82)	1.44 (1.16-1.80)	1.55 (1.24-1.95)

*Normotensive was defined as systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg and without antihypertensive drug treatment.

†Adjusted for age, study year and sex.

‡Adjusted for age, study year, sex, education, and alcohol consumption.

§Adjusted for age, study year, sex, education, alcohol consumption, total cholesterol, history of myocardial infarction, history of valvular heart disease and history of diabetes.

CI = confidence interval; HR = hazard ratio.

treated, controlled group without a healthy lifestyle; and 10] hypertensive, treated, uncontrolled group without a healthy lifestyle) were 1.00, 1.50 (95% CI 1.20-1.88), 1.54(95% CI 1.18-2.01), 2.24 (95% CI 1.39-3.64), 1.91(95% CI 1.46-2.50), 2.12 (95% CI 1.65-2.72), 2.68 (95% CI 2.14-3.35), 3.05 (95% CI 2.37-3.93), 2.27 (95% CI 1.25-4.11), and 3.21 (95% CI 2.47-4.18) (P_{trend} <0.001), respectively. Further adjustment for total cholesterol, and histories of myocardial infarction, valvular heart disease, and diabetes did not appreciably alter the results.

Table 16 presents the comparison between the association of engaging in a healthy lifestyle with the risk of HF and the association of using antihypertensive drugs with the risk of HF. In the multivariable-adjusted analyses (model 2), hypertensive subjects who used antihypertensive drugs but did not engage in a healthy lifestyle had a significantly higher risk of HF (HR 2.10; 95% CI 1.68-2.63) than hypertensive subjects who did not use antihypertensive drug but engaged in a healthy lifestyle. Hypertensive subjects who did not use antihypertensive drugs and did not engage in a healthy lifestyle had a significant higher risk of HF (HR 1.44; 95% CI 1.16-1.80) compared with hypertensive subjects who used antihypertensive drug and engaged in a healthy lifestyle. Further adjustment for total cholesterol, and histories of myocardial infarction, valvular heart disease, and diabetes affected these results only slightly.

5.4 Discussion

The results of the present study suggest that the risk of HF was higher in untreated unaware, aware treated and controlled, and aware treated and uncontrolled hypertensive people than in normotensive people. Treated hypertensive subjects without a healthy lifestyle

had a higher risk of incident HF than untreated hypertensive subjects with a healthy lifestyle; however, treated hypertensive subjects with a healthy lifestyle had a lower risk of incident HF than untreated hypertensive subjects without a healthy lifestyle.

High blood pressure has long been shown as an independent risk factor for HF risk. Levy et al.(Levy et al., 1996) showed that hypertensive subjects had an increased risk of HF. In 2003, Haider et al.(Haider et al., 2003) demonstrated that elevated blood pressure was an independent risk factor for incident HF. In addition to the evidence provided by observational studies, numerous clinical trials have shown that blood pressure reduction achieved with pharmacotherapy is associated with a decreased risk of HF in hypertensive subjects.(Dahlof et al., 2005; Julius et al., 2004; Liu et al., 2005; Wing et al., 2003) The current study supports the findings of the previous studies and adds additional information: despite antihypertensive drug treatment and adequate control of hypertension, the risk of HF remained relatively high. This stresses the importance of adequate primary prevention and more effective early management of hypertension.

Modifiable lifestyle factors like smoking,(Djousse et al., 2009; Eriksson et al., 1989b; He et al., 2001; Hoffman et al., 1994; Wilhelmsen et al., 2001) physical activity,(Djousse et al., 2009; Hu et al., 2010b; Kenchaiah et al., 2009; Wang et al., 2010b) adiposity,(Djousse et al., 2009; Hu et al., 2010b; Kenchaiah et al., 2002; Kenchaiah et al., 2009; Levitan et al., 2009a) ,and dietary intake,(Djousse et al., 2009; Wang et al., 2011b) have been shown to be independently associated with the risk of HF in various studies. Also, we found that there was a graded inverse association between the number of healthy lifestyle factors and the risk of HF in this Finnish population.(Wang et al., 2011a) In the current study, we assessed the joint

effects of hypertensive status (awareness, antihypertensive drug treatment, blood pressure control status) and lifestyle pattern on the risk of HF. We found that subjects engaged in a healthy lifestyle at baseline generally had lower risk of HF than those did not, and this association could be found in normotensive subjects as well as hypertensive subjects regardless of their awareness, and treatment.

Numerous trials have investigated the effect of antihypertensive drug treatment on HF risk in hypertensive subjects.(Dahlof et al., 2005; Julius et al., 2004; Liu et al., 2005; Wing et al., 2003) However, no previous study had studied the differences in HF risk among hypertensive people by antihypertensive treatment and lifestyle status. In the current study, we first showed that the risk of incident HF was higher in the treated hypertensive subjects without a healthy lifestyle than in the untreated hypertensive subjects with a healthy lifestyle. Since one may argue that patients with treated hypertension might be more likely to have severe hypertension than hypertensive patients with a healthy lifestyle, it cannot be concluded that a healthy lifestyle may be more effective in preventing HF than antihypertensive treatment in hypertensive subjects. In order to understand this possible bias, we did additional analyses to compare the incident HF risk between the treated hypertensive subjects who engaged in a healthy lifestyle and the untreated hypertensive subjects who did not engage in a healthy lifestyle, and still found that a healthy lifestyle may be associated with a further reduced HF risk in hypertensive people. Our finding supports the statement of one recent review: “use a combination of lifestyle changes and pharmacotherapy to achieve systolic blood pressure goals and to achieve the ultimate goal of reducing end-organ damage”.(Baliga, 2007) In 2010, the AHA published the AHA 2020 impact goals: “By

2020, to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%".(Lloyd-Jones et al., 2010) In order to achieve this goal, a new concept–cardiovascular health was introduced by the AHA.(Lloyd-Jones et al., 2010) Seven metrics including not only health factor but also health behaviours were proposed to be monitored to determine the changing prevalence of cardiovascular health status.(Lloyd-Jones et al., 2010) Our results support the fundamental expansion of prevention efforts proposed by the AHA.

There are several strengths and limitations in our study. First, a major strength of the study is the large number of both men and women from a homogeneous population who participated in the study. Second, the follow-up time was sufficiently long to ascertain a large number of HF endpoint events. Finally, we also carried out additional analyses excluding the subjects who died during the first two years of follow-up to avoid a potential bias due to a severe disease at baseline. A limitation of our study is that information on self-reported physical activity, smoking habits, vegetable consumption, alcohol consumption and antihypertensive drug treatment was recorded only once at baseline. We have no data on possible changes in these factors during the follow-up. However, the misclassification of the levels of these factors during the follow-up is most probably not systematically related to the outcome, but may weaken the observed association. In addition, we cannot completely either exclude the effects of residual confounding due to measurement error in the assessment of confounding factors, or some unmeasured dietary factors.

In conclusion, the present study demonstrates that the risk of HF increased in hypertensive people despite antihypertensive drug treatment and adequate control of hypertension, which

emphasized the importance of adequate primary prevention efforts. In addition, our study also indicated that lifestyle intervention may be at least as effective in preventing HF as antihypertensive treatment in hypertensive subjects, which justifies the inclusion of ideal health behavioral factors into the definition of cardiovascular health of the AHA.(Lloyd-Jones et al., 2010) The results may also help encourage people at high HF risk to engage in health lifestyle changes while initiating medical therapy aiming at good blood pressure control.

CHAPTER 6. CONCLUSIONS

It is generally believed that lifestyle interventions are beneficial in preventing and treating cardiovascular diseases. However, scientific evidence is lacking regarding the effect of engaging in healthy lifestyle in preventing heart failure (HF). In this dissertation: it is demonstrated that 1) moderate and high levels of occupational or leisure-time physical activity are associated with a reduced risk of HF; 2) coffee consumption is not detrimental to HF patients; 3) maintaining a BMI ≤25 kg/m2, consuming vegetable ≥3 times a week, abstaining from smoking and engaging in moderate or high level of physical activity were individually and jointly associated with a decreased risk of HF among both men and women; and 4) lifestyle intervention may be at least as effective in preventing HF as antihypertensive treatment in hypertensive subjects. These results justified the recommendations, such as increasing physical activity, eating healthy diet, stopping smoking and maintaining optimal body weight, made by health-care professionals to the general public. Also, the result of our studies may help to encourage people of high heart failure risk to attend lifestyle intervention programs targeting reducing heart failure risk factors or preventing heart failure, and to motivate health-care professionals to increase uptake to these programs.

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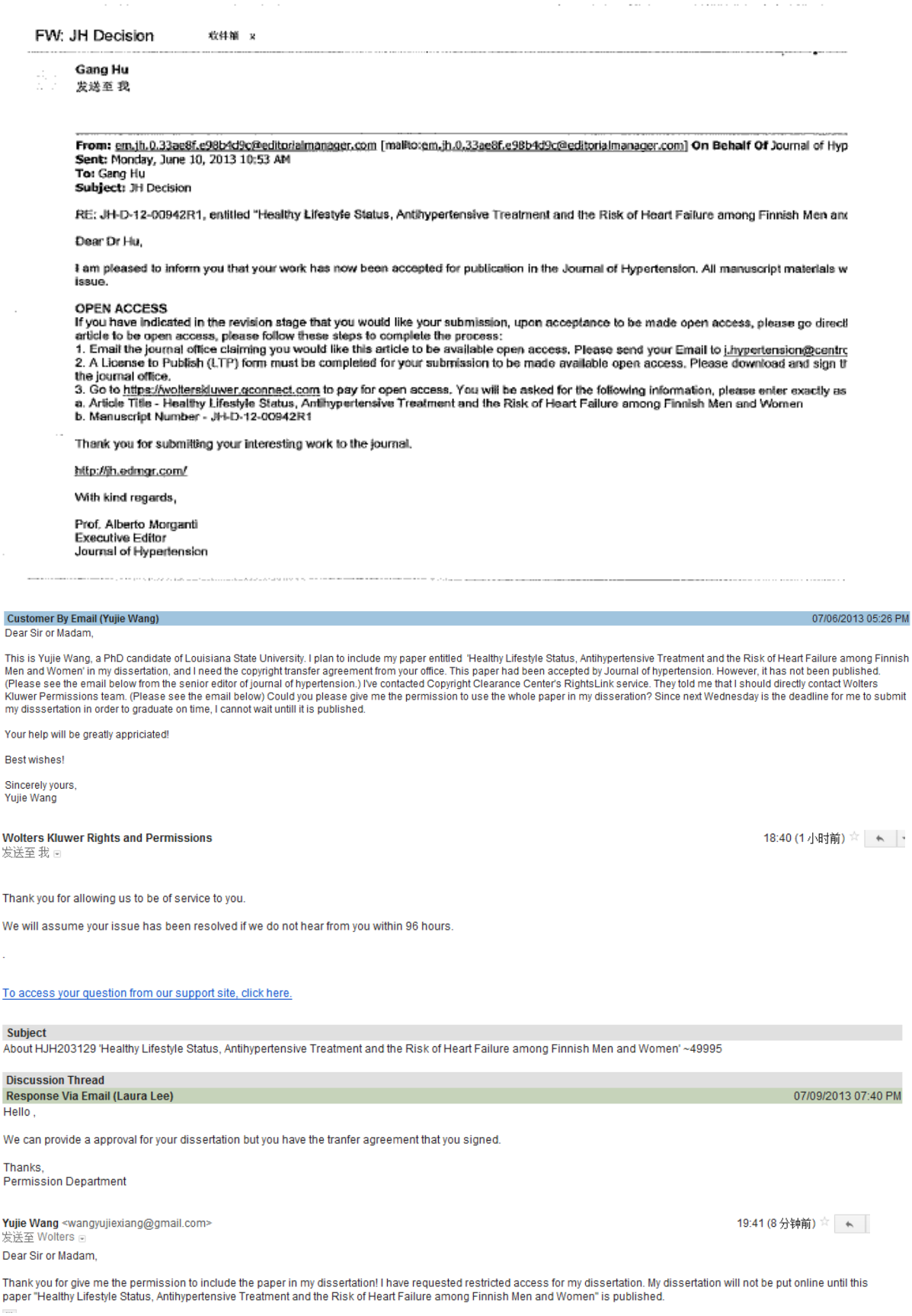

FW: JH Decision

Gang Hu
发送至 我

From: em.jh.0.33ae8f.e98b4d9c@editorialmanager.com [mailto:em.jh.0.33ae8f.e98b4d9c@editorialmanager.com] **On Behalf Of** Journal of Hyp
Sent: Monday, June 10, 2013 10:53 AM
To: Gang Hu
Subject: JH Decision

RE: JH-D-12-00942R1, entitled "Healthy Lifestyle Status, Antihypertensive Treatment and the Risk of Heart Failure among Finnish Men an

Dear Dr Hu,

I am pleased to inform you that your work has now been accepted for publication in the Journal of Hypertension. All manuscript materials w
issue.

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b. Manuscript Number - JH-D-12-00942R1

Thank you for submitting your interesting work to the journal.

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With kind regards,

Prof. Alberto Morganti
Executive Editor
Journal of Hypertension

Customer By Email (Yujie Wang) 07/06/2013 05:26 PM

Dear Sir or Madam,

This is Yujie Wang, a PhD candidate of Louisiana State University. I plan to include my paper entitled 'Healthy Lifestyle Status, Antihypertensive Treatment and the Risk of Heart Failure among Finnish Men and Women' in my dissertation, and I need the copyright transfer agreement from your office. This paper had been accepted by Journal of hypertension. However, it has not been published. (Please see the email below from the senior editor of journal of hypertension.) I've contacted Copyright Clearance Center's RightsLink service. They told me that I should directly contact Wolters Kluwer Permissions team. (Please see the email below) Could you please give me the permission to use the whole paper in my disseration? Since next Wednesday is the deadline for me to submit my disssertation in order to graduate on time, I cannot wait untill it is published.

Your help will be greatly appriciated!

Best wishes!

Sincerely yours,
Yujie Wang

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About HJH203129 'Healthy Lifestyle Status, Antihypertensive Treatment and the Risk of Heart Failure among Finnish Men and Women' ~49995

Discussion Thread
Response Via Email (Laura Lee) 07/09/2013 07:40 PM

Hello ,

We can provide a approval for your dissertation but you have the tranfer agreement that you signed.

Thanks,
Permission Department

Yujie Wang <wangyujiexiang@gmail.com> 19:41 (8 分钟前)
发送至 Wolters

Dear Sir or Madam,

Thank you for give me the permission to include the paper in my dissertation! I have requested restricted access for my dissertation. My dissertation will not be put online until this paper "Healthy Lifestyle Status, Antihypertensive Treatment and the Risk of Heart Failure among Finnish Men and Women" is published.

VITA

Yujie Wang was born in Chongqing, People's Republic of China. She is the only daughter of Kaihua Wang and Minfeng Gao. Yujie received her Bachelor of Science Degree in Pharmacy in July 2003 from Chongqing Medical University, China. From 2003 to 2005, she worked in the Pharmacy Department of Chongqing Medical University as an Assistant Experimentalist. She was the only graduate selected to work in the department that year. In 2005, she was successfully admitted into a master program in pharmaceutics in Shanghai Jiao Tong University based on her excellent performance in the national entrance examination for master degree and her work experience. During her two-and-a-half year study, she participated in research projects, involving method development for the quality control of an important botanical drug under development. Yujie began a master's program in the spring of 2010 at Louisiana State University in the School of Human Ecology with a concentration in human nutrition and food. She got her master's degree in this program in August, 2011. At the end of 2012, Yujie got a master of applied statistics from Louisiana State University. During her study in Louisiana State University, Yujie published 20 peer-reviewed journal articles (11 first author papers, 9 co-author papers). After graduation as a PhD, Yujie will continue working in nutritional epidemiology field and try her best to contribute to people's health.